New *N*-Heterocyclic Carbene Ligands and Their Applications in Organometallic Catalysis

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Zusammenfassung

Die Entwicklung der N-heterozyklischen Carbene (NHCs) als Liganden für Übergangsmetallkatalysatoren hat sich als sehr fruchtbar auf dem Gebiet der homogenen Katalyse erwiesen. Um diese Ligandenfamilie für die Katalyse zu erweitern, stellt diese Dissertation eine Reihe von neuen NHC-Liganden her, die substituierte Naphthylgruppen als Seitenketten aufweisen. Durch das Einführen geeigneter Stereozentren im N-heterocyclischen Teil dieser Liganden können optisch reine Liganden hergestellt werden. Die Liganden wurden sowohl in normalen als auch in asymmetrischen, Metal-katalytischen Umwandlungen verwendet und diese Dissertation beinhaltet neue Katalysemethoden für die Bildung verschiedener C-C Bindungen.

Kapitel 2 beschreibt die Synthese und Charakterisierung einer neuen Klasse von leicht zugänglichen NHCs mit gesättigten und ungesättigten N-Heterozyklen, die alkylierte Naphthyl Seitenketten beinhalten. Durch sorgfältige Abstimmung und Erweiterung der Substituenten an den Positionen 2 oder 2,7 der Naphthyl Seitenketten wurden NHC-Moleküle erzeugt, die praktisch nur die anti-Konformation annehmen. Wenn sowohl die 2- und 7-Positionen der Napthyleinheiten mit Cyclooctylgruppen substituiert werden, kann ein bemerkenswert aktiver Palladiumkatalysator synthetisiert werden, der bei Raumtemperatur Suzuki-Miyaura Reaktionen von sterisch äusserst anprussvollen Arylgruppen zulässt. Kapitel 3 befasst sich mit der Synthese und katalytischen Verwendung von chiralen NHC Liganden. Diese wurden durch Einlagerung von C_2-symmetrischen Diaminen in ihren heterozyklischen Ring erhalten. Wenn die Position 2 des Naphthylring mit einer 3-Pentylgruppe belegt wird, entstehen drei diastereomere NHC Salze und deren Palladiumkomplexe konnten leicht abgetrennt werden. Ihr Einsatz als Katalysatoren bei der α-Arylierung von Amiden wurde in der Synthese von chiralen 3-Allyl-3-aryl-Oxindolen getestet. Des Weiteren wurde ein diastereomerenreines NHC Salz durch die Einführung einer Cyclooctylgruppe in Position 2 der Naphtylketten erhalten. Der entsprechende Palladiumkomplex wurde in einer neuen, Palladium-katalysierten asymmetrischen Synthese von 3-Aryl-3-Fluor-Oxindolen verwendet und ergab Produkte mit ausgezeichneten Enantioselektivitäten. Kapitel 4 beschreibt die asymmetrische Ringöffnung oxabizyklischer Alkene mit Grignard-Reagenzien unter Verwendung

desselben diasteromerenreinen NHC Liganden. Der dazu verwendete chirale NHC-Cu-Komplex katalysiert die asymmetrische Reaktion zwischen einer Reihe von oxabicyclischen Alkenen und alkylgrignard Reagenzien und die resultierenden Produkte lagen in guten Ausbeuten, hohen *ee*- und Diastereoselektivitäten vor. Phenyl- und allylgrignard Reagenzien konnten auch verwendet werden und das Endprodukt wurde in guten Ausbeuten und moderaten *ee'*s erhalten. In Kapitel 5 beschreiben wir die Synthese eines neuen NHC Liganden mit einem chiralen N-Heterozyklus und Naphthyl Seitenketten mit 4-Heptylsubstituenten in der Position 2. Die Imidazoliniumsalze lagen als drei verschiedene Isomere vor. Diastereomerenreine Palladiumkomplexe dieser Liganden wurden nach einfacher Säulenchromatographie erhalten. Eine der resultierenden Verbindungen (*Sa,Sa*-[Pd]) wurde in der asymmetrischen Suzuki-Miyaura und Kumada Kupplungsreaktion getestet, die zu chiralen Biarylen in hohen Ausbeuten und mäßigen Enantioselektivitäten führte.

Abstract

The recent development of *N*-heterocyclic carbenes (NHCs) as ligands for transition metal catalysts has proved to be very fruitful in the field of homogeneous catalysis. In order to expand the family of versatile NHC systems for catalysis, this dissertation introduces a series of new NHC ligands that incorporate substituted naphthyl groups as side chains. These new NHC ligands could be made optically pure by introducing appropriate stereocenters on the N-heterocyclic part of the ligand. The ligands were used in both normal as well as asymmetric catalytic transformations and this thesis covers catalysis involving various C-C formation strategies.

Chapter 2 describes the synthesis and characterization of a new class of easily accessible NHCs with saturated and unsaturated N-heterocycles that incorporate alkylated naphthyl side chains. Through carefully tuning and enlarging the substituents on positions 2 or 2,7 of the naphthyl side chains, NHC molecules were generated that display a very strong preference to assume only the *anti* conformation. We found that when both 2- and 7-positions were substituted with cyclooctyl groups and a saturated N-heterocycle was employed, a remarkably active palladium precatalyst for the Suzuki-Miyaura coupling giving tetra-*ortho*-substituted biaryls at room temperature was formed. In Chapter 3, the NHC study was expanded to their chiral counterparts by introducing the chiral regime of C_2-symmetric diamines into their heterocyclic backbone. When the 2-position of the naphthyl ring was substituted with 3-pentyl groups, three diastereomers were generated and their palladium complexes were easily separated. Their use as catalysts was tested in the α-arylation of amides for the synthesis of chiral 3-allyl-3-aryl-oxindoles. Furthermore, a diastereomerically pure NHC salt was obtained by the introduction of a cyclooctyl group to the 2-position. Its palladium complex was tested in a new, palladium-catalyzed asymmetric synthesis of 3-aryl-3-fluoro-oxindoles and excellent enantioselectivities were obtained. Chapter 4 discloses the asymmetric ring-opening of oxabicyclic alkenes with Grignard reagents using the same diasteromerically pure NHC ligand. The preformed chiral NHC-copper complex catalyzes the asymmetric reaction between a series of oxabicyclic alkenes and alkyl Grignard reagents and the resulting products were afforded in good yields, high *ee*'s and excellent diastereoselectivities. Phenyl and allyl Grignard reagents were also tolerated giving

the final product in good yields and moderate *ee*'s. In chapter 5, we report the synthesis of a new NHC ligand with a chiral *N*-heterocycle and naphthyl side chains having 4-heptyl in the 2-position. The imidazolinium salts showed the existence of three different isomers in these NHC structures. Diastereomerically pure palladium complexes incorporating these ligands were obtained after simple chromatography. One of the resulting compounds (*SaSa*-[Pd]) was tested in the asymmetric Suzuki-Miyaura and Kumada coupling that formed atropisomeric biaryls in high yields and moderate enantioselectivities.

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Chapter 1

Introduction

In chemistry, a carbene is a divalent carbon species linked to two adjacent groups by a covalent bond and it possesses two non-bonding electrons and six valence electrons. The general formula is RR'C**:**, but the carbon can instead be double-bonded to one group. Carbenes are classified as either singlets or triplets depending upon their electronic structure. Singlet carbenes are spin-paired and the molecule adopts an sp^2 hybrid structure. Triplet carbenes have two unpaired electrons. They may be either linear or bent, i.e. *sp* or sp^2 hybridized, respectively (**Figure 1**). Most carbenes have a nonlinear triplet ground state, except for those with nitrogen, oxygen, or sulfur atoms, and halides directly bonded to the divalent carbon.[1]

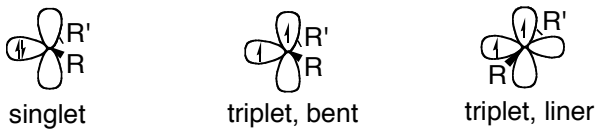


Figure 1. Singlet and triplet carbenes.

At the beginning of the carbene chemistry, carbenes were considered to be too reactive to be isolated. However, their use in organic chemistry dates back to the 1950s when Döring used chloroform to generate dichlorocarbene which could be added to olefins.[2] In 1964, the reactive species was introduced to organometallic chemistry by Fischer who reported the first carbene complex $W(CO)_5[(=C(OCH_3)(CH_3)]$.[3] From then on, the majority of carbene research was focused on transition metal carbene complexes. Metal carbene complexes are often classified into two types. The "Schrock carbenes", named after Richard R. Schrock, are characterized by a more nucleophilic carbene carbon center; this species typically features higher valent metals (**Figure 2**).[4] "Fischer carbenes", named after Ernst Otto Fischer, feature strong π-acceptors at the metal and are electrophilic at the carbene carbon atom. A Fischer carbene is predominantly a σ-donor via the lone pair, but the empty π orbital on carbon is also a weak acceptor for π back donation from the M(dπ) orbitals (**Figure 2**).[3]

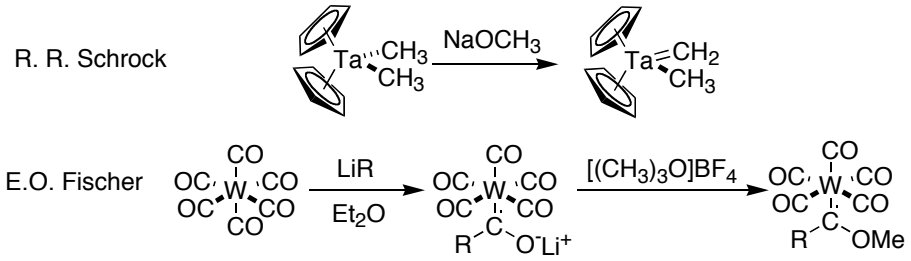


Figure 2. Schrock and Fischer carbene

The nature of the substituents bound to the carbene carbon have profound effects on the stability, reactivity and electronics of the carbenes.[5] The concept that carbenes could be stabilized by π interactions with donor atoms was first developed by Wanzlick.[6] When at least one of the donor atoms is nitrogen and are part of a cyclic structure, the stabilized carbene system is known as an *N*-heterocyclic carbene or NHC. The main contribution to the stability of NHCs comes from the strong σ-electron-withdrawing and the π-electrons-donating character of nitrogen atoms. The existence of stable NHCs was proposed by Wanzlick *et al.* at the beginning of the 1960s,[6,7] and supported by the first independent reports by Öfele and Wanzlick of transition metal complexes containing NHC ligands around 1970 (**Figure 3**).[8]

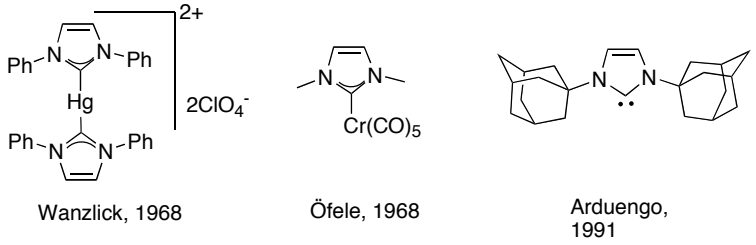
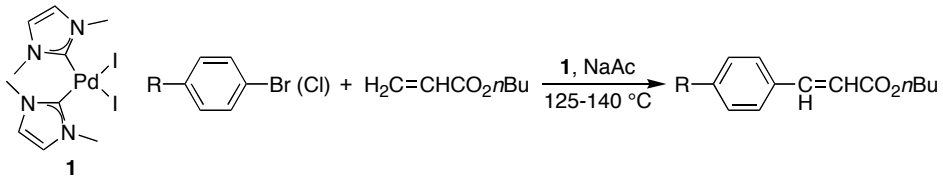


Figure 3. The earliest NHC transition metal complexes and the first isolated free carbene

However, no diaminocarbene had been isolated with relatively high stability, i.e. without tendency to dimerize until the milestone report of Arduengo *et al.* of a stable crystalline carbene in 1991.[9] The first stable NHC was based on the imidazol-2-ylidene ring and had adamantyl groups as substituents on the N atoms (IAd, **Figure 3**), enjoying thermodynamic as well as kinetic stability in the absence of oxygen and moisture. Since Arduengo's report, interest in the area has greatly intensified. Due to their strong σ-electron-donating properties, NHC ligands form stronger bonds with

metal centers than most classical ligands, such as phosphines, thus giving transition metal complexes that are generally resistant to decomposition and can thus be used as precatalysts without an excess of ligand.



Scheme 1. First example of organometallic catalysis using NHC

Early on in the development of NHC moieties as ancillary ligands, it was recognized that they could serve as alternatives to the polular phosphines in transition-metal-catalysis. However, in the last two decades, the exponential growth of the number of applications of NHCs in catalysis has promoted them to the status of "well-established ligands in catalysis". The potential of this class of compounds to serve as spectator ligands in transition-metal complexes was recognized in 1995 by Herrmann *et al.*, using the NHC-Pd complex **1** to promote Heck reactions (**Scheme 1**).[10] Soon thereafter, the exploitation of the remarkable potential of NHC ligands in (asymmetric) catalysis began.[11] The most important example is the ruthenium metathesis catalyst developed by Grubbs and co-workers, for which the Nobel Prize was awarded.[12] Replacement of one of the two tricyclohexylphosphine ligands in the generation I Grubbs catalyst with the bulky carbene SIMes led to significant improvements in terms of catalyst stability, activity, and substrate range in subsequent generations (**Figure 4**).

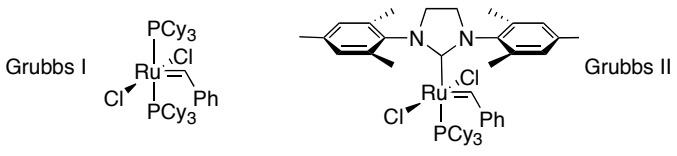


Figure 4. The 1st and 2nd generation Grubbs catalysts

In the passed two decades a great number of NHC-bearing catalysts with very different structures have been designed (**Figure 5**). In many cases these catalysts exhibited better activity than the corresponding phosphine-based catalysts for a

particular application. Besides the above-mentioned Ru-catalyzed metathesis of olefins, they also showed numerous applications in other transformations.[11]

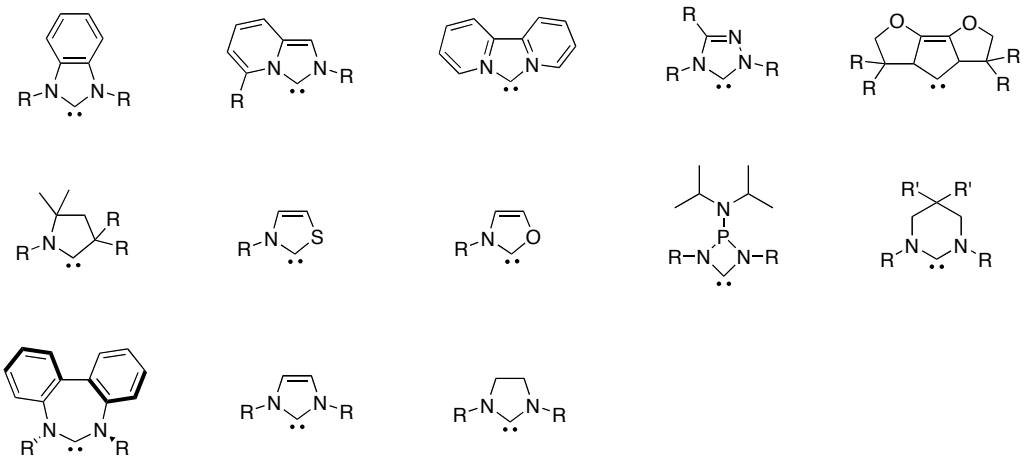


Figure 5. The general stuctures of different types of NHCs

The introduction of N-heterocyclic carbenes as ligands for transition metal catalysts and as organic catalysts on their own has put this class of compounds at the forefront of current research efforts.[11,12b-c] Whereas hundreds of NHCs with various structural motifs (Figure 5) have been synthesized and tested in catalysis, bulky, monodentate aryl-substituted imidazol-2-ylidenes (2,4,6-mesityl-substituted IMes and 2,6-isopropylphenyl-substituted IPr) and their saturated imidazolin-2-ylidene counterparts (SIMes and SIPr) still remain the only ligands that represent a truly viable alternative to phosphines, both in terms of versatility and reactivity (**Figure 6**). Presumably, the perpendicular arrangement of the aryl side chains, combined with the steric bulk on the aromatic rings, leads to a situation where these ligands confer stability to unsaturated and reactive metal centers during catalysis and where decomposition of the catalyst through unwanted metal–ligand interactions is rarely observed. Equally important for their widespread use and success is the simple fact that IMes/SIMes and IPr/SIPr are stable as free carbenes, making them easy to handle and manipulate. In this context, it is of note that most structures based on saturated imidazolin-2-ylidenes dimerize readily to give enetetramines. This renders saturated NHCs considerably less amenable to catalysis and restricts access to stable modifications of this ligand class. In fact, the tendency of saturated NHCs towards dimerization is so pronounced that very few stable imidazolin-2-ylidenes are known in the literature.[13,14]

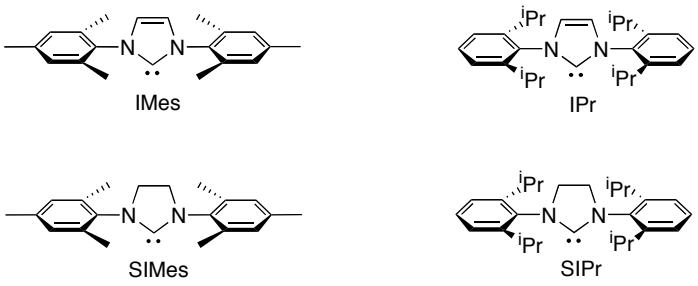


Figure 6. The most common NHCs

The *H* atoms in positions 4, 5 of the saturated imidazolin-2-ylidene ring is a key structural feature for the introduction of asymmetry in the NHC ring, which opens the door to the use of chiral NHCs in asymmetric synthesis. In 2001, Grubbs introduced the chirality to the imidazole ring by using the commercially available chiral diamines (*1R*, *2R*)-diphenylethylenediamine and (*1R*, *2R*)-diaminocyclohexane (**2** and **3**, Figure 7).[15] In 2010, Blechert designed and synthesized a monosubstituted carbene **4** (Figure 7) which showed good selectivity in the asymmetric ring opening cross metathesis (AROCM). [16] Recently, Murakami reported the synthesis of the novel chiral *N*-heterocyclic carbene ligands **5** with rigid backbones and applied them to the palladium-catalyzed enantioselective intramolecular α-arylation of amides (Figure 7).[17]

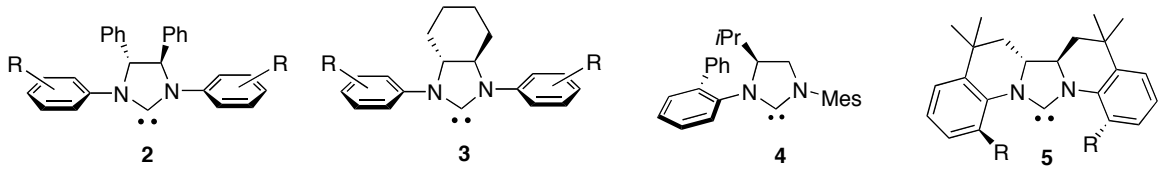
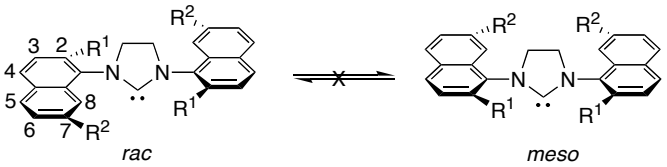


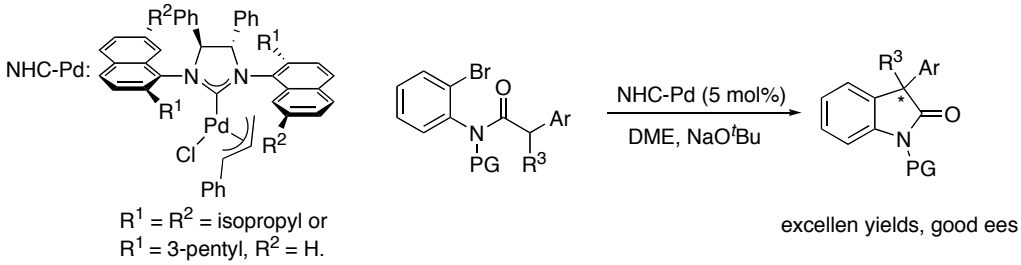
Figure 7. Chiral NHC ligands by introducing chirality to 4 and/or 5 positions of the N-heterocycle

In 2008, we have described the synthesis of a series of saturated NHCs that incorporate substituted naphthyl side chains. In both the NHC salts and the free carbenes, introduction of substituted naphthyl side chains gives rise to C_2-symmetric *(rac)* and C_s-symmetric (*meso*) atropisomers which can not interconvert into each other (**Scheme 2**). We demonstrated that this new naphthyl-based NHC ligand family presents high reactivities in palladium-based coupling reactions, in ruthenium-based metathesis and in the organocatalytic ring-opening alkylation of epoxide.[18]



Scheme 2. Atropisomers in NHCs incorporating substituted naphthyl side chains

We have shown that the introduction of a chiral *N*-heterocycle in this NHC system led to three diastereomers in the salt stage. Pure palladium complexes incorporating these ligands were obtained after successful separation of their diastereomeric mixtures. These obtained palladium complexes were tested in the α-arylation of amides to generate 3-aryl-3-methyl/allyl chiral oxindoles (**Scheme 3**). We found that generally the (*Ra,Ra*)-isomer gave the best result in terms of reactivities and selecetivities.[19]



Scheme 3. (*Ra,Ra*)-isomer in α-arylations of amides

We reasoned that the fluxionality of the resulting ligands might be tunable by adjusting the size of the substituents at the 2- and 7-positions of the naphthyls. In this way, the ratio of the isomers in the NHC salts can be modified and the reactivity and selectivity of the corresponding complexes will be increased.

The objective of the work described in this dissertation is to develop this new family of promising NHC ligands. Their use in homogeneous catalysis, especially in asymmetric catalysis, will lead to the discovery of new reactivity and/or high selectivity in novel and challenging transformations.

In chapter 2, we highlight the dramatic increase of the reactivity of such NHC-containing catalyst systems by putting a cyclooctyl group in the 2- position of the

naphthyl side chain. We disclose the first catalyst system which is able to efficiently catalyze Suzuki-Miyaura coupling at room temperature forming bulky tetra-*ortho*-substituted biaryls from bromides and chlorides. Advanced DFT calculations show how the ligand's steric properties, which are inherently associated to its symmetry, leave two of four quadrants that represent the ligands overall steric environment relatively open.

Based on the work disclosed in chapter 2, we then expanded the new NHC family to chiral NHC ligands for asymmetric catalysis by introducing a chiral backbone (chapter 3). Based on the chiral regime of C_2-symmetric starting diamines, the naphthyl-based chiral NHC ligands were readily prepared. Unsuspectedly, there is only one diastereomer existing in the corresponding NHC salt. The enantiopure NHC ligand can then be transferred onto a palladium complex, which was tested in the asymmetric synthesis of 3-aryl-3-fluoro-oxindoles. The biologically important oxindoles were obtained with good yields (up to 94%) and excellent enantioselectivities (up to >99% ee). DFT calculations are offered to rationalize the excellent selectivity.

Encouraged by the good result from chapter 3, we studied this ligand in another asymmetric transformation, namely the ring-opening of oxabicyclic alkenes (chapter 4). For doing that, we synthesized a copper complex containing this NHC ligand whose structure was elucidated by an X-ray diffraction study. The enantioselective ring-opening of oxabicyclic alkenes with Grignard reagents afforded the products in high yields, high enantioselectivities and excellent *trans* diastereoselectivities. We also report two rare examples of asymmetric ring-opening with phenyl- and allyl-Grignard reagents, respectively.

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Chapter 2

Room-Temperature Synthesis of Tetra-*ortho*-Substituted Biaryls via NHC-Palladium Catalyzed Suzuki-Miyaura Couplings

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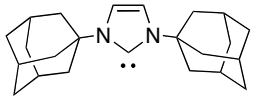
2.1 Abstract

We describe the synthesis of a series of new saturated and unsaturated NHCs that incorporate alkylated naphthyl side chains. Through carefully tuning and enlarging the substituents on positions 2 or 2,7 of the naphthyl side chains, NHC molecules were generated that display a very strong preference to assume only the *anti* conformation. We found that when both 2- and 7- positions were substituted with cyclooctyl groups and a saturated heterocycle was employed, an NHC ligand is created that in combination with a palladium precursor results in a remarkably active catalyst for Suzuki-Miyaura couplings. This represents the first catalyst system that can promote the Suzuki-Miyaura coupling to form bulky tetra-*ortho*-substituted biaryls from aryl bromides and chlorides at room temperature. The key point is the introduction of a C_2-symmetric NHC ligand with appropriately substituted naphthyl side chains. Advanced DFT calculations show that two of the four quadrants in the ligand are relatively open and the other two are hindered, a factor that results in the excellent activity.

2.2 Introduction

The affirmation of *N*-heterocyclic carbenes as ligands for transition metals catalysts and as organic catalysts proved to be an important innovation in the field of catalysis.[1,2] Especially useful in this respect (so far) have been *N*-heterocyclic carbenes with five-membered heterocyclic structures first reported by Arduengo et al., such as imidazol-2-ylidene **1** and the saturated heterocyclic imidazolidin-2-ylidene derivatives **2**.[3,4]



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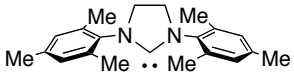


2

Whereas dozens of structural variations of NHCs **1** and **2** exist nowadays, the overwhelming majority incorporates the unsaturated central *N*-heterocycle of **1**. The reason for this lies in the surprisingly different stabilities of unsaturated and saturated NHCs. While dimerization of aromatically stabilized *N*-heterocyclic carbenes of type **1** is thermodynamically unfavorable even for small *N*-substituents like Me,[5,6] formation of the enetetramine dimer of **2** occurs readily. This renders saturated NHCs

considerably less amenable to catalysis and restricts access to stable modifications of this ligand class, as the substituents at the nitrogen atoms need to be very bulky. The demarcation line separating stable from unstable carbenes may be established and lies somewhere between ^{t}Bu/^{i}Pr for *N*-alkyl substituents and Mes/Ph for aromatic side chains.[7-9]

In catalysis, work in the last decade has shown that monodentate NHCs with bulky, aryl-substituted side chains are the overall most successful design. As such, 2,4,6-mesityl-substituted IMes and 2,6-isopropylphenyl-substituted IPr and their saturated imidazolin-2-ylidene counterparts (SIMes and SIPr) still remain the only ligands that represent a truly viable alternative to phosphines, in terms of both versatility and reactivity.

Our entry in this fascinating field of research began with the design and the synthesis of stable saturated free carbenes that feature substituted naphthyl side chains.[10] We reasoned that this architecture would mimic well the original SIMes and SIPr ligand systems, offering at the same time a scaffold that is less hindered in proximity to the potential metal binding site and that can be functionalized more readily with a wide range of substituents, tuning both its steric and electronic properties (Figure 1).

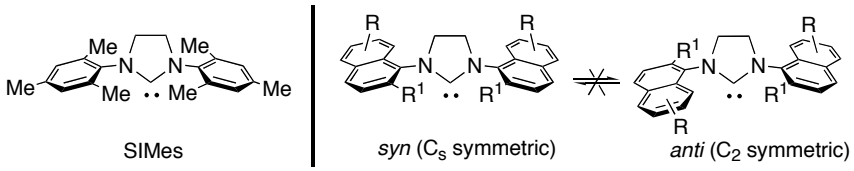


Figure 1. Imidazolin-2-ylidenes with phenyl (left) and naphthyl (right) side chains

The substitution pattern confers to these molecules a high degree of conformational stability, generating in solution a mixture of *anti* and *syn* conformers (Figure 1). Detailed NMR study on the fluxional behavior of this class of carbenes showed that, even at high temperature, interconversion between the conformers is not possible if sterically demanding substituents are present in position 2 of the naphthyl side chains (R^1 in Figure 1).[11] This encouraged us to attempt the separation of the *syn* and *anti* isomers for some of these molecules but this process, up to now, has been successful only when the NHC was incorporated into a stable metal complex. Recent studies

performed in our laboratory also indicated that, for some type of metal-catalyzed transformations, organometallic catalysts containing NHCs in the *anti* isomeric form perform better then the ones in the *syn* form.[12]

These reasons prompted us to attempt the synthesis of molecules displaying a conformational preference for only one of the two isomers. Herein, we describe the synthesis of a series of new saturated NHCs that incorporate alkylated naphthyl side chains. With the aim of minimizing the formation of the *syn* isomer, we selected a bulky, linear alkyl substitutent as well as more rigid, cyclic alkyl derivatives of various sizes.

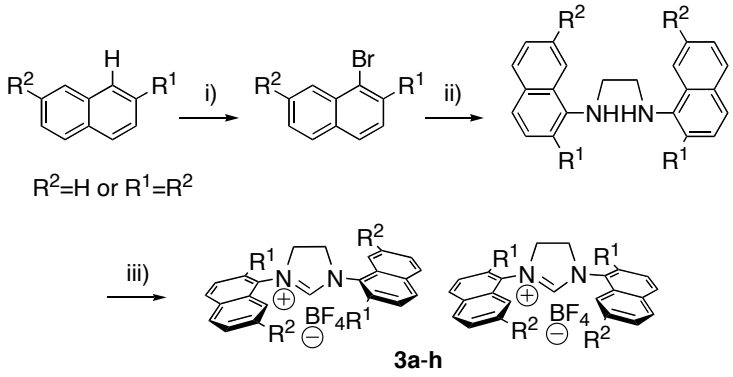
Transition metal catalyzed cross couplings have become some of the most powerful and widely used method to construct C-C bonds.[13] Among them, the Suzuki-Miyaura coupling,[14] has emerged as a particularly attractive and practical tool for synthetic organic chemistry.[15] Indeed, within the last decade, several limitations of this methodology have been successfully adressed by using bulky, electron-rich monodentate phosphines or sterically demanding NHC ligands.[16] One of the few challenges remaining in the Suzuki-Miyaura coupling reaction involve transformations with sterically demanding substrates that lead to tetra-*ortho*-substituted products. Especially in cases where aryl chlorides are used, the relatively poor nucleophilicity of the arylboron reagents results in diminished catalytic activities.[17] In 2004, Glorius and coworkers showed for the first time that aryl chlorides can indeed be coupled to aryl boronic acids to generate such tetra-*ortho*-substituted biaryls at elevated temperature (110 °C) by employing a very bulky, yet flexible derivative of their bioxazoline-derived NHC ligands in combination with a Pd(II) metal salt.[18] More recently (2009) and following the same concept of 'flexible steric bulk' of the NHC ligand, Organ and coworkers used complex Pd-PEPPSI-IPent as the catalyst for the Suzuki-Miyaura couplings to form bulky tetra-*ortho*-substituted biaryls at milder conditions (65 °C).[19] Since then, various other ligand systems have been shown to effect similar couplings involving aryl chlorides when appropriate heating is employed.[20] To date, systems that work at room temperature have not been reported for the construction of these important tetra-*ortho*-substituted biaryl structures via the Suzuki-Miyaura coupling.[21]

Herein we describe the application of our NHC ligand systems in the Palladium-catalyzed Suzuki-Miyaura couplings to give tetra-*ortho* substituted biaryl and present

conclusive evidence on the reasons leading to their superior behavior in these reactions.

2.3 Results and Discussion

The synthesis of the NHC salt is relatively straightforward and generally high yields were obtained. Bromination of the alkylnaphthalenes (Scheme 1) was achieved in all cases with excellent yield and with perfect regioselectivity for position 1 of the naphthalene when performing the reaction at low temperature (-78 °C) using equimolar amounts of Br_2 with CH_2Cl_2 as the solvent. The following double Buchwald-Hartwig coupling with ethylenediamine in the presence of $Pd_2(dba)_3$ (5 mol%), (±)-BINAP (12 mol%) and NaO*t*Bu (2.1 eq) generated diamines in good yields and high purity after chromatographic purification. Ring-closing of the respective diamines in the presence of triethyl orthoformate as reagent/solvent and NH_4BF_4 furnished the desired imidazolinium salts **3a**-**h** in generally good yields (Scheme 1). Table 1 reports the yields for the ring formation step and the ratio of conformers (*syn* respectively *anti*) observed. To have a more general overview, data concerning naphthyl-based NHC salts already reported by our group are also shown.[10]



i) Br_2, CH_2Cl_2, -78°C; ii) ethylenediamine, $Pd_2(dba)_3$, *rac*-BINAP, NaO^{t}Bu, toluene, 110°C;
iii) NH_4BF_4, HCO_2H (cat.), $HC(OEt)_3$, 100°C,

Scheme 1. General synthesis of the NHC salts featuring naphthyl side chains

Tendentially, yields are slightly lower when starting with diamines that contain very bulky substituents in position 2 of the naphthalene moiety (Table 1, entries 1-7) and with precursor molecules with 2,7-dialkylated precursors (Table 1, entires 8-13), probably reflecting an increasingly difficult approach of the nucleophile in the reaction sequence. Concerning the *syn*/*anti*-ratio of the NHC salts, we note that when

small alkyl groups and linear, flexible alkyl chains are present in positions 2 or 2,7 of naphthalene rings (entries 1-3 and 8-9 in Table 1), the two possible conformers were

Table 1. Yields and *syn-anti* ratio for compounds **3a-3h**, **3d'**, **3h'** and previously reported imidazolinium salts containing naphthalene wingtips

entry	imidazolinium salt	yield (%)	*syn-anti* ratio[a]
1	(2)-SIMeNap·HBF_4[b]	88	50 : 50
2	(2)-SIPrNap·HBF_4[b]	60	50 : 50
3	(2)-SIHeptNap·HBF_4 (**3a**)	75	43 : 57
4	(2)-SICypentNap·HBF_4 (**3b**)	75	50 : 50
5	(2)-SICyNap·HBF_4[b]	78	27 : 72
6	(2)-SICyheptNap·HBF_4 (**3c**)	58	22 : 78
7	(2)-SICyoctNap·HBF_4 (**3d**)	60	17 : 83
8	(2,7)-SIMeNap·HBF_4[b]	80	50 : 50
9	(2,7)-SIPrNap·HBF_4[b]	56	50 : 50
10	(2,7)-SICypentNap·HBF_4 (**3e**)	35	50 : 50
11	(2,7)-SICyNap·HBF_4 (**3f**)	50	5 : 95
12	(2,7)-SICyheptNap·HBF_4 (**3g**)	48	15 : 85
13	(2,7)-SICyoctNap·HBF_4 (**3h**)	29	10 : 90
14	(2)-ICyoctNap·HCl (**3d'**)	30	0 : 100
15	(2,7)-ICyoctNap·HCl (**3h'**)	46	8 : 92

[a] The ratios were deduced from NMR analysis. [b] These compounds have been reported before (ref. 10)

formed in almost equal amounts. The same trend was observed when a small, cyclic ring was present in position 2 or 2,7 (entry 4 and 10 in Table 1). Increasing progressively the bulkiness of the cyclic alkyl substituents (entries 5-7 in Table 1) favors the formation of the *anti* conformer. When large cyclic alkyl groups are present in both positions 2 and 7, the *syn* conformer becomes strongly disfavored and, in the best case (entry 11), a 95:5 *anti-syn* ratio is obtained.

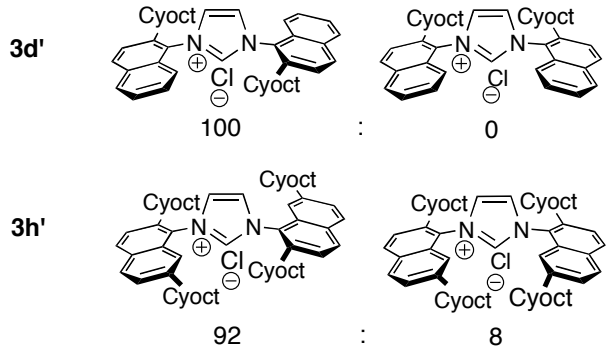
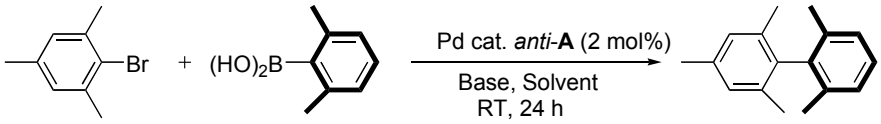


Figure 2. Unsaturated NHC salts

Since using cyclooctyl group as the substitution at 2- and 7- positions lead to the remarkable preference of *anti* conformer (entries 7 and 13), the unsaturated carbene salts **3d'** and **3h'** were also synthesized (Figure 2). As expected, the **3h** analogue **3h'** presented 92% of the *anti* isomer. Surprisingly and to our delight, salt **3d'**, which contains the unsaturated backbone and 2-position substituted naphthyl side chains, showed exclusively the formation of the *anti* isomer.

Reaction of NHC ligands with both saturated and unsaturated *N*-heterocycles incorporating 2- or 2,7-cyclooctyl groups on the naphthalene side chains with Pd(cin)Cl dimer (cin = cinnamyl) and appropriate workup gave the four complexes (*anti*-**A**, **B**, **C**, **D**) depicted in Table 3 in good yields as single isomers (*anti*-configured)

Table 2. Base and solvent screening for biaryl synthesis using *anti*-**A**.[a]

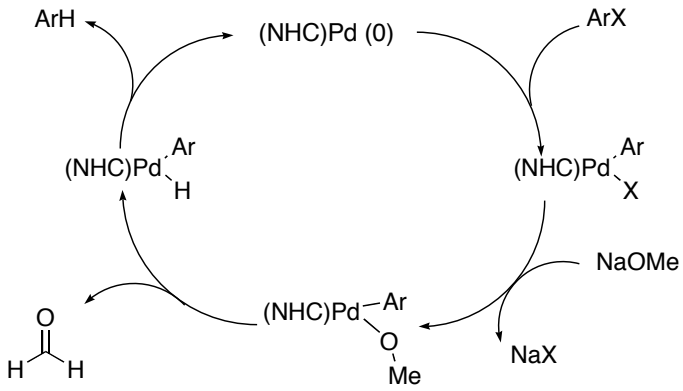


Entry	Base	Solvent	Conversion (%)	Yield (%)
1	KO*t*Bu	Toluene	100	100
2	LiO*t*Bu	Toluene	0	0
3	NaO*t*Bu	Toluene	13	11
4	NaOMe	Toluene	72	7
5	KHMDS	Toluene	0	0
6	K_3PO_4	Toluene	<5	<5
7	KOH	Toluene	<5	<2
8	K_2CO_3	Toluene	0	0
9	KO*t*Bu	Benzene	100	100
10	KO*t*Bu	Dioxane	10	7
11	KO*t*Bu	DME	0	0
12	KO*t*Bu	THF	0	0
13	KO*t*Bu	Ether	37	36
14	KO*t*Bu	CH_2Cl_2	30	13
15	KO*t*Bu	*t*BuOH	8	7
16	KO*t*Bu	*i*PrOH	100	0

[a] Reaction conditions: 0.125 mmol (1 equiv) of bromide, 1.5 equiv of boronic acid, 2.5 equiv of base, 2 mol% of Pd complex, in solvent (1ml), RT, 24h; GC yield with dodecane as internal standard.

At the outset of our study, we wanted to find out the optimized condition for the Suzuki-Miyaura coupling. Using 2 mol% of *anti*-**A** as the catalyst, the choice of base

and solvent in the reaction between 2,4,6-trimethylphenyl bromide and 2,6-dimethylphenyl boronic acid were screened at room temperature and the results are summarized in Table 2. When toluene was used as the solvent, KO*t*Bu showed to be the best base by giving full conversion and quantitative yield by GC analysis (entry 1). The use of other bases such as LiO*t*Bu, NaO*t*Bu, KHMDS, K_3PO_4, KOH and K_2CO_3 afforded no or little conversion (entries 2-3, entries 5-8). NaOMe as the base gave good conversion (72%, entry 4), however, with low yield (7%). This can be attributed to the side reaction of dehalogenation whose mechanism is demonstrated in Scheme 2. The alkoxide attacks at the metal center followed by β-hydride elimination and then reductive elimination of the arene from the metal(II)-hydride complex occurs. The solvent screen revealed that benzene gave the same excellent result as toluene showing full conversion and quantitative yield (entry 9). Because of the toxicity of benzene, we chose toluene as the solvent for the rest of the study. Ethereal solvents such as dioxane, DME and THF showed little reactivity (entries 10-12) while diethyl ether gave moderate conversion and yield (entry 13). Using isopropanol in combination with KO*t*Bu decomposed the starting material completely via dehalogenation (entry 16). KO*i*Pr from deprotonation of *i*PrOH with KO*t*Bu played the same role as NaOMe displayed in Scheme 2. The importance of the presence of an α-proton in the alkoxide in the dehalogenation can be highlighted by the comparison of *t*BuOH and *i*PrOH, where the former did not afford any dehalogenation product (entry 15).

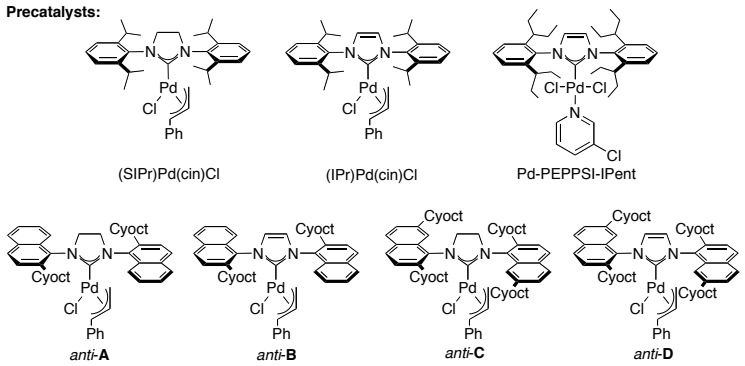


Scheme 2. Mechanism of NHC-Pd catalyzed dehalogenation

To explore the effect of these new NHC ligands on biaryl formation in more difficult Suzuki-Miyaura couplings (coupling with chloride), we chose the reaction

between 2,4,6-trimethylphenyl chloride and 2,6-dimethylphenyl boronic acid (Table 3). Under optimized reaction conditions, the four new catalyst systems were benchmarked against their commercially available, SIPr/IPr-modified congeners (Nolan's catalysts) as well as Organ's Pd-PEPPSI-IPent system, currently the most powerful precatalyst for such transformations. At room temperature, these reference systems resulted in low product yields (entries 1-5, GC yields). In entries 4/5, we used Organ's previously reported reaction conditions,[7] which deteriorated the reaction outcome. Gratifyingly, all catalysts incorporating the new NHC structures showed higher conversions/yields than the benchmark systems. Among the four substructures tested, *anti*-**C** clearly stands out as being particularly effective as it shows both high conversions and yields at room temperature.

Table 3. Screening of precatalysts in a representative example of room temperature Suzuki-Miyaura coupling.[a]



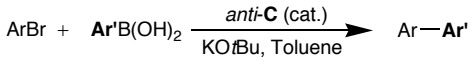
Entry	Pd-complex	Conversion (%)	Yield (%)
1	(SIPr)Pd(cin)Cl	39	35
2	(IPr)Pd(cin)Cl	40	33
3	Pd-PEPPSI-IPent	33	29
4	Pd-PEPPSI-IPent	20	14[b]
5	Pd-PEPPSI-IPent	7	>5[c]
6	*anti*-**A**	45	39
7	*anti*-**B**	60	51
8	*anti*-**C**	95	90
9	*anti*-**D**	65	61

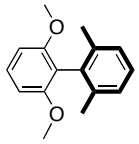
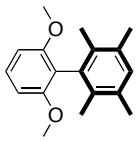
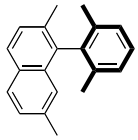
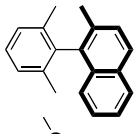
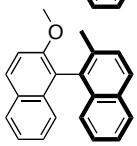
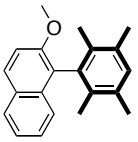
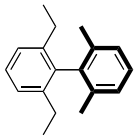
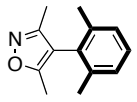
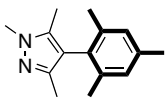
[a] Conditions: 25 ºC, toluene (1 ml), 24 h, Ar-Cl (0.125 mmol), Ar-B(OH)$_2$ (0.250 mmol), KO*t*Bu (0.312 mmol), 2 mol% Pd-cat.; conversions/yields determined by GC with internal standard; [b] KO*t*Bu (0.375 mmol), *t*BuOH (0.5 mL), 4 Å M.S.; [c] KOH (0.375 mmol), dioxane (0.5 ml).

We then proceeded in evaluating the coupling of a variety of hindered aryl bromides (Table 4) and aryl chlorides (Table 5) employing precatalyst *anti*-**C**. As can

be seen from the data reported in Table 4, high isolated product yields were normally obtained at room temperature within short reaction times when employing aryl bromides. In entry 2, where the coupling proceeded very slowly at room temperature, slight heating (65°C) was applied, leading to a dramatic increase in reactions rates. Indeed, entry 5 shows that as little as 0.2 mol% of catalyst suffices for the reaction to

Table 4. Suzuki-Miyaura couplings generating tetra-*ortho*-substituted products starting with aryl bromides catalyzed by *anti*-**C**.[a]



Entry	Ar—**Ar'**	Pd [mol%]	Time (h)	Yield (%)
1		2	12	96
2		2	72	80
3		1	2	96[b]
4		0.5	3	92[b][c]
5		0.2	12	97[b][c]
6		2	15	92
7		2	12	85
8		1	16	95
9		2	10	91
10		2	18	67
11		2	20	70
12		2	20	88

[a] Conditions: 25 °C, toluene (3.2 ml), Ar-Br (0.4 mmol), Ar-B(OH)$_2$ (0.6 mmol), KO*t*Bu (1.0 mmol); isolated products yields; [b] 65 °C; [c] toluene (2 ml).

go to completion. More sterically demanding 2,6-diethylphenylbromide could also be coupled with 2,6-dimethylphenyl boronic acid at room temperature in acceptable yield (entry 10). Two representative tetrasubstituted heterobiaryls were also successfully synthesized in good yields (entries 11, 12).

Table 5 shows examples for the synthesis of tetra-*ortho*-substituted biaryls starting from the corresponding aryl chlorides. Again, a variety of hindered biaryls with a broad substitution pattern were prepared smoothly at room temperature. In two cases when sterically demanding and electron-rich arylchlorides are used, slight heating was necessary for complete conversion (entries 2, 3). In cases where reactivity was good at room temperature, slight heating permitted the use of much lower catalyst loadings (entries 8, 12, 13). Using the corresponding NHC/Pd(dba)$_2$ precatalyst system instead of *anti*-**C** completely surpresses the coupling reaction at room temperature (entries 4 *vs* 5), meaning that the catalytically active 12-electron NHC-Pd^0 complex is not generated in the former case. Interestingly, the present system also displayed excellent chemoselectivity, favoring Suzuki-Miyaura couplings over the Heck reaction scenario (entries 15, 16). Precatalyst *anti*-**C** also promotes less difficult Suzuki-Miyaura coupling reactions, as evidenced from data gathered in entry 18. The last two entries in Table 5 also highlight just how different the reactivities are when moving from a tri- to a tetra-*ortho*-substituted coupling product.

This last observation, together with the uniquely high reactivity of *anti*-**C**, prompted us to investigate the present catalytic system further. As a first approach, we

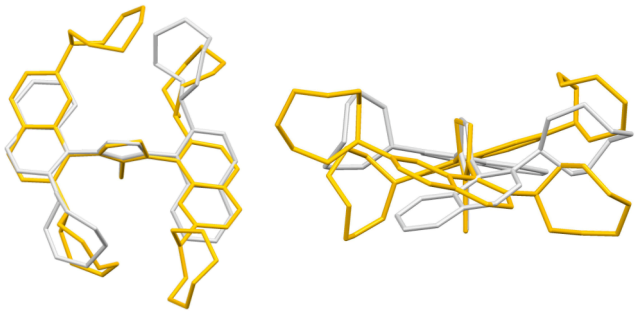
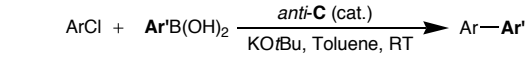
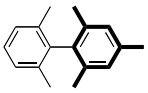
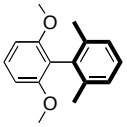
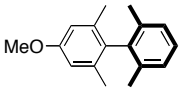
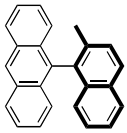
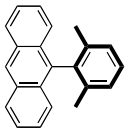
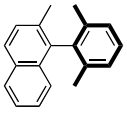
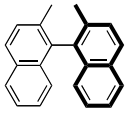
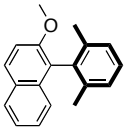
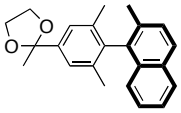
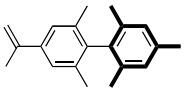
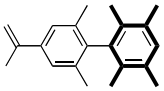
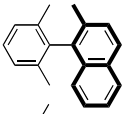
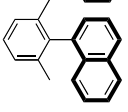


Figure 3. Overlay of the molecular structures of *anti*-**B** (grey) and *anti*-**C** (yellow). Cinnamyl, chloride and hydrogens omitted for clarity.

Table 5. Suzuki-Miyaura couplings generating tetra-*ortho*-substituted products starting with aryl chlorides catalyzed by *anti*-**C**.[a]



Entry	Ar—**Ar'**	Pd [mol%]	Time (h)	Yield (%)
1		2	8	78
2		1	8	80[b]
3		2	2	72[b]
4		2	20	92
5		2	20	<10[c]
6		2	20	86
7		2	8	89
8		0.5	1.5	85[b][d]
9		2	16	82
10		1	10	90
11		1	1	91[b]
12		0.5	1.5	88[b][d]
13		0.2	7	80[b][d]
14		2	20	78
15		2	18	71
16		2	24	72
17		2	12	91
18		0.05	15	80[e]

[a] Conditions: 25 °C, Toluene (3.2 ml), Ar-Cl (0.4 mmol), Ar-B(OH)$_2$ (0.8 mmol), KO*t*Bu (1.0 mmol), *anti*-**C**; isolated products yields; [b] 65 °C; [c] 2 mol% Pd(dba)$_2$/(2,7)-SICyoctNap; [d] 2 ml toluene; [e] 25 °C, *i*PrOH (0.5 mL), Ar-Cl (0.5 mmol), Ar-B(OH)$_2$ (1.1 eq), 0.05 mol % *anti*-**C**, KO*t*Bu (1.3 eq).

grew single crystals of *anti*-**C** and of the unsaturated NHC-Pd derivative that lacks the 7-cyclooctyl groups on the naphthalene units (*anti*-**B**) in order to compare their structures in the solid state (Figure 3).[22]

One notes that these *anti*-configured NHCs lead to idealized C_2-symmetry of the ligand framework, in contrast to the commonly used IPr/SIPr or Organ's IPent ligands, which result in structures of C_{2v} symmetry. Between the NHC ligands in *anti*-**B** and *anti*-**C**, the main difference resides in the way the naphthyl side chains are twisted with respect to the central metal atom. The introduction of additional steric crowding (7-cyclooctyl) leads to a structure in *anti*-**C** where the 2-cyclooctyl groups point into the space occupied by the metal.[23]

To further understand the difference between the catalytically preferred NHC ligand of *anti*-(2,7)-SICyoctNap and the more established SIPr ligand, we calculated the buried $\%V_{Bur}$ of the two NHC ligands,[24,25] The simple $\%V_{Bur}$ of the NHC ligands in *anti*-**C** (41.5%) and (SIPr)Pd(cin)Cl (34.9%) show that our ligand is bulkier than SIPr. That an overall more bulky NHC ligand behaves better in catalysis involving sterically more demanding substrates is not unusual and the term of 'flexible steric bulk' has been introduced to account for this phenomenon.[16b,18a,19] At least in a catalytic coupling scheme that follows the classical path (i.e. no secondary reactivity/decomposition), this concept is nevertheless at odds with what one would expect. For this reason we decided to perform a more detailed analysis by evaluating the $\%V_{Bur}$ in the single quadrants around the Pd center and we plotted them as steric contour maps (Figure 4) for both (SIPr)Pd(cin)Cl (left) and *anti*-**C** (right), [24a,d,e] Splitting the total $\%V_{Bur}$ into quadrant contributions quantifies any asymmetry in the way the ligand wraps around the metal.[26] Within this approach, the quadrant $\%V_{Bur}$ of SIPr is rather constant ($\%V_{Bur}$ ~35%), while the quadrant $\%V_{Bur}$ values of *anti*-(2,7)-SICyoctNap are largely different. Two quadrants heavily hindered (top left and bottom right, $\%V_{Bur}$ ~53%), two quadrants clearly more open (top right and bottom left, $\%V_{Bur}$ ~30%) creating a groove that possibly can host bulky substrates.

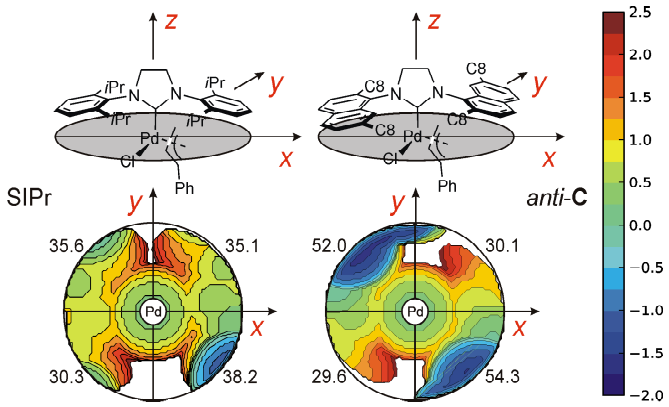


Figure 4. Steric maps of the NHC ligands in (SIPr)Pd(cin)Cl and *anti*-**C** complexes.

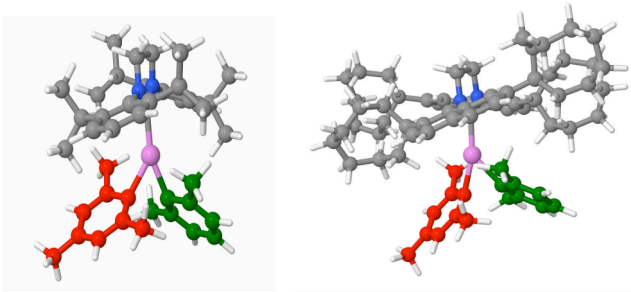


Figure 5. Transition state of the reductive elimination for (SIPr)Pd(Ar)(Ar') (left) and [*anti*-(2,7)-SICyoctNap]Pd(Ar)(Ar') (right).

We therefore turned our attention to the catalytic step where sterics play the crucial role, namely the transmetallated (NHC)Pd(Ar)(Ar') [where Ar = 2,4,6-trimethylphenyl and Ar' = 2,6-dimethylphenyl] intermediate and the following reductive elimination. We first calculated the total energy of the system when going from the starting naked (NHC)Pd(0) species (set at 0 kcal/mol), to the transmetallated (NHC)Pd(Ar)(Ar') intermediate according to equation **1**.

$$(NHC)Pd + ArCl + Ar'B(OH)_2 + KO\textit{t}Bu \rightarrow (NHC)Pd(Ar)(Ar') + KCl + \textit{t}BuOB(OH)_2 \quad (\mathbf{1})$$

This approach eliminates the specific way the two aryl moieties are loaded onto the metal. Loading of these two aryls onto the (NHC)Pd(0) species (eq 1), is favored for both (SIPr)Pd (by 23.8 kcal/mol) and [*anti*-(2,7)-SICyoctNap]Pd (by 30.7 kcal/mol). This in turn means that the groove created by the *anti*-(2,7)-SICyoctNap ligand is able to more readily accommodate (by 6.9 kcal/mol) the bulky aryl fragments than SIPr. An identical preference (6.9 kcal/mol) is also calculated at the level of the following

transition state (overall 15 kcal/mol higher in energy) leading to the coupled Ar-Ar' product. Representations of these transition states for both complexes show a distorted T-shaped geometry (**Figure 5**). As already evidenced by the steric contour map of Figure 2, the structures shown in Figure 3 perfectly illustrates how the open quadrants in *anti*-(2,7)-SICyoctNap are able to host the *ortho* methyl groups of the aryl substituent *cis* to the NHC ligand. Differently, in presence of the SIPr ligand the same *ortho* methyl groups interact repulsively with the NHC ligand. In other words, the special steric characteristics of *anti*-(2,7)-SICyoctNap facilitate loading and releasing of the bulky aryl groups from the metal by creating a groove that is able to accomodate the *ortho* methyl groups of the aryl moieties. Together with the overall very bulky nature of this ligand, this translates into the clearly superior catalytic performance that we see in these Suzuki-Miyaura couplings.

2.4 Conclusion

In summary, we disclose the first catalyst system that is able to efficiently perform the Suzuki-Miyaura coupling to form bulky tetra-*ortho*-substituted biaryls from aryl bromides and chlorides at room temperature. The central feature of the catalyst sees the introduction of a C_2-symmetric NHC ligand with appropriately substituted naphthyl side chains. This simple modification to the well-known ligand systems allows for a dramatic increase in catalytic performance in these difficult Suzuki-Miyaura coupling reactions, apparently leaving the already high activity in less demanding coupling reactions unaffected. Advanced DFT calculations show that the 'flexible steric bulk' of our ligand is inherently given by its symmetry, which leaves two of the four quadrants relatively open, thus enhancing the reactivity of the system with respect to the crucial, sterically demanding NHC-Pd(Ar)(Ar') intermediate and the following reductive elimination step.

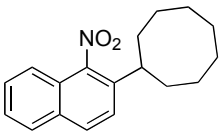
Acknowledgment. R. D. holds an Alfred Werner Assistant Professorship and thanks the foundation for generous financial support. Support for this work was provided by SNF (grant to L. W.) and the Roche Research Foundation (grant to E. D.).

2.5 Experimental Part

2.5.1 General: All reactions were carried out using standard Schlenk or glovebox

(Mecaplex or Innovative Technology) techniques under nitrogen. KO*t*Bu was used after sublimation. 2,6-Diisopropylchlorobenzene[27] and 2,4,6-triisopropylbromobenzene[28] were prepared according to literature. Imidazolinium salts were prepared according to our previous report.[29] All other reagents were used as received unless otherwise noted. Solvents were purchased in the best quality available, degassed by purging thoroughly with nitrogen and dried over molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Solvents for NMR spectroscopy were degassed with nitrogen and dried over molecular sieves. NMR spectra were collected on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra were calibrated to the residual 1H and 13C of the solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). High-resolution electrospray ionization mass spectrometry was performed on a *FinniganMAT 900* (Finnigan MAT95, San Jose, CA; USA) double-focusing magnetic sector mass spectrometer (geometry BE). GC analysis was done on a ThermoQuest TraceGC2000. GC-MS analysis was done on a Finnigan Voyager GC8000 Top. X-ray crystallography was performed on a NoniusKappaCCDarea-detector diffractometer using graphite-monochromated Mo Kradiation (= 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler.

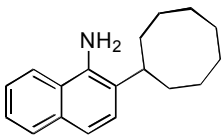
2-Cyclooctyl-1-nitronaphthalene. 4.40 g (18.5 mmol) 2-cyclooctylnaphthalene and



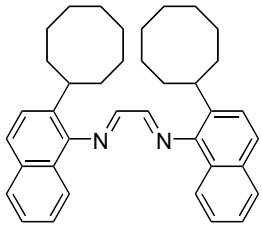
13 g dry $MgSO_4$ were added into 50 ml of CH_2Cl_2. Then 1.30 ml of fuming nitric acid was added dropwise in 1h. Let the mixture gradully warm to room temperature and keep stirring overnight. After filtration, the solution was concentrated and then refluxed in 150 ml ethylacetate in the precense of 16.6 g $SnCl_2 \bullet 2H_2O$ for 2h. After the solution was cooled to r.t., the solvent was evaporated in vacuo and the residue was chromatographed on silica gel (n-hexane:CH_2Cl_2 3:1) giving 1.80 g (35%) of the title compound as a yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.88 (d, *J* =8.7 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.56 (td, *J* = 6.8, 1.1 Hz, 1H), 7.50 (td, *J* = 6.8, 1.1 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 2.98-2.92 (m, 1H), 1.87-1.54 (m, 14H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz):146.32, 138.71, 132.19, 130.77, 128.61, 128.07, 126.89, 124.94, 124.50, 121.68, 39.28, 34.92, 26.85, 26.65, 26.31. HRMS (EI): m/z: calcd for

$C_{18}H_{21}NO_2[M]^+$: 283.1572; found: 283.1570.

1-Amino-2-cyclooctylnaphthalene. 2-cyclooctyl-1-nitronaphthalene (3.0 g, 10.6 mmol) was dissolved in 100 mL of technical grade methanol. This solution was transferred into a high pressure autoclave and Pd on carbon (5% wt. Pd, 300 mg) was added. After purging with formier gas and hydrogen, the autoclave was charged with 50 bar of H_2. After stirring at room temperature for 48 hours, the pressure was released and the reaction mixture filtered through celite. After concentration, the residue was purified by flash column chromatography on silica-gel (n-hexane:CH_2Cl_2 1:1) to get title product as a white solid (2.50 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.80 (d, J = 7.7, 1H), 7.78 (d, J = 7.2, 1H), 7.48-7.40 (m, 2H), 7.35 (s, 2H), 4.16 (s, 2H), 3.01-2.96 (m, 1H), 1.94-1.68 (m, 14H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 136.97, 132.76, 128.74, 128.59, 125.82, 125.12, 124.08, 120.91, 118.98, 38.79, 33.64, 27.16, 26.74, 26.71. HRMS (EI): *m/z* : calcd for $C_{18}H_{23}N$ $[M]^+$: 253.1830; found: 253.1830.

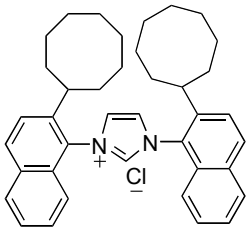


***N,N'*-Bis(2-cyclooctylnaphthalene)ethylenediimine.** 1-Amino-2-cyclooctylnaphthalene (2.28 g, 9.0 mmol) and 6 drops of gracial acid were disssolved in 25 ml of technical grade methanol at 50°C. Then aqueous glyoxal solution (40% wt, 653 mg) in 6 ml of methanol was added dropwise by syringe in 30 min. Let the mixture cool down to r.t. and keep stirring overnight. The yellow precipitate was filtered off, washed with cold methanol and dried under vacuum to lead to the title compound as a yellow powder (1.7 g, 72%).^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.45 (s, 2H), 7.84-7.78 (m, 4H), 7.68 (d, J = 8.7 Hz, 2H), 7.49-7.45 (m, 6H), 3.25-3.20 (m, 2H), 1.87-1.63 (m, 28H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 164.99, 144.39, 134.55, 132.53, 130.35, 128.10, 126.33, 125.74, 125.69, 125.62, 123.43, 37.59, 35.29, 27.41, 26.95, 26.62. HRMS (EI): *m/z* : calcd for $C_{38}H_{45}N_2$ $[M+1]^+$: 529.35773; found: 529.35787.



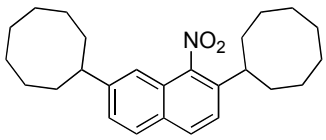
1,3-Bis(2-cyclooctylnaphthalen-1-yl)imidazolium chloride. Paraformaldehyde (48 mg, 1.60 mmol) was added to 0.60 ml of a 4 N solution of HCl in dioxane (2.4 mmol). The mixture was stirred and gently warmed until complete dissolution of the solid. In another flask, *N,N'*-Bis(2-cyclooctylnaphthalene)ethylenediimine (430 mg,

0.81 mmol) was gently warmed in 4 ml THF until it completely disolved. At room



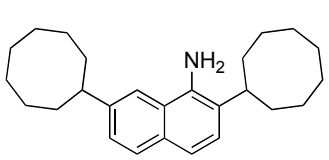
temperature, the paraformaldehyde solution was added dropwise into the diimine solution slowly. The mixture was stirred overnight and the precipitate was filtered and then disolved in 2 ml of MeOH. 20 ml of ether was added into this solution to get the precipitate again. The precipitate was collected and dry under vacuum. The title compound was obtained as a white solid (140 mg, 30% yield, only one isomer was observed). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.46 (s, 1H), 8.86 (s, 1H), 8.34 (d, J = 8.4 Hz, 2H), 8.20 (d, J = 7.8 Hz, 2H), 7.83-7.67 (m, 6H), 7.16 (d, J = 7.9 Hz, 2H), 2.64 (br, 2H), 2.04-1.46 (m, 28H). ^{13}C {^{1}H} NMR (DMSO-d_6, 125 MHz): 145.66, 140.88, 132.47, 132.26, 129.21, 129.16, 129.12, 127.65, 127.40, 126.22, 125.90, 120.65, 49.07, 39.02, 35.12, 34.75, 26.83, 26.61, 26.28, 26.04, 25.95. HRMS (ESI): *m/z* : calcd for $C_{39}H_{45}N_2$ [M-Cl]$^{+}$: 541.35773; found: 541.35761.

2,7-Dicyclooctyl-1-nitronaphthalene. 3.60 g (10.3 mmol) 2,7-



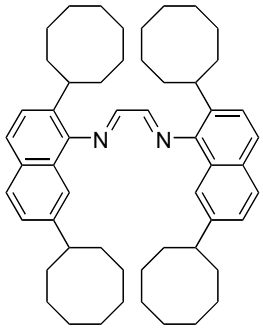
dicyclooctylnaphthalene and 12 g dry $MgSO_4$ were added into 120 ml of CH_2Cl_2. Then 2.40 ml of nitric acid (66 %) was added dropwise into this suspension in 20 min at 0 °C. Allowed the mixture gradully warm to room temperature and keep stirring for 1.5 h. After filtration, the solution was concentrated and the residue was dissolved in 120 ml ethylacetate and the obtained solution was refluxed in the precense of 7.0 g $SnCl_2$•$2H_2O$ for 2h. After the solution was cooled to r.t., the solvent was evaporated in vacuo and the residue was chromatographed on silica gel (n-hexane:CH_2Cl_2 10:1) giving 2.80 g (70%) of the title compound as a yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.82 (d, J =8.6 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.39-7.24 (m, 3H), 2.93-2.88 (m, 2H), 1.84-1.58 (m, 28H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz):151.19, 146.22, 138.59, 130.79, 130.40, 128.13, 127.26, 124.62, 123.91, 118.38, 45.33, 39.35, 34.92, 34.87, 27.20, 26.82, 26.70, 26.62, 26.32, 26.28. HRMS (EI): m/z: calcd for $C_{26}H_{35}NO_2$[M]$^{+}$: 393.2668; found: 393.2667.

1-Amino-2,7-dicyclooctylnaphthalene. 2,7-dicyclooctyl-1-nitronaphthalene (2.52 g, 6.40 mmol) was dissolved in 50 mL of CH_2Cl_2. This solution was transferred into a high pressure autoclave and the solvent was evaporated by purging N_2 flow on the



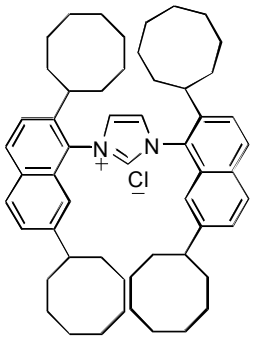
above of the sulution. 100 ml of technical grade methanol and Pd on carbon (5% wt. Pd, 300 mg) were added and the autoclave was closed. After purging with formier gas and hydrogen, the autoclave was charged with 50 bar of H_2. After stirring at 50 °C for 48 hours, the pressure was released and the reaction mixture was filtered through Celite. After concentration, the residue was purified by flash column chromatography on silica-gel (n-hexane:CH_2Cl_2 3:1) to get title product as a white solid (1.40 g, 60%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.66 (d, J = 8.4, 1H), 7.55 (s, 1H), 7.26-7.21 (m, 3H), 4.11 (s, 2H), 2.95-2.89 (m, 2H), 1.92-1.60 (m, 28H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 147.37, 136.60, 131.15, 128.89, 128.66, 125.48, 124.91, 124.12, 118.86, 117.79, 45.52, 35.12, 33.63, 27.22, 26.71, 26.67, 26.39. HRMS (EI): *m/z* : calcd for $C_{26}H_{37}N$ $[M]^+$: 363.2926; found: 363.2923.

***N*,*N*'-Bis(2,7-dicyclooctylnaphthalene)ethylenediimine.** 1-Amino-2,7-

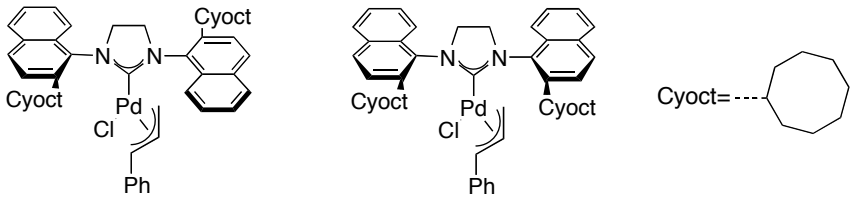


dicyclooctylnaphthalene (1.05 g, 2.88 mmol) and 4 drops of gracial acid were disssolved in 90 ml of technical grade methanol at 70°C. Then aqueous glyoxal solution (40% wt, 210 mg) in 6 ml of methanol was added dropwise by syringe in 20 min. Let the mixture stir at 70 °C overnight. The yellow precipitate was filtered off, washed with cold methanol and dried under vacuum to lead to the title compound as a yellow powder (0.96 g, 89%).^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.45 (s, 2H),7.74 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.56 (s, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.34 (dd, J = 8.4, 1.6 Hz), 3.18-3.14 (m, 2H), 2.90-2.86 (m, 2H), 1.86-1.56 (m, 56H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 164.78, 148.62, 144.06, 134.43, 130.94, 128.12, 126.06, 125.92, 125.49, 124.93, 120.37, 45.66, 38.11, 35.27, 35.12, 33.69, 27.25, 27.20, 27.13, 26.95, 26.67, 26.64, 26.42. HRMS (ESI): *m/z* : calcd for $C_{54}H_{73}N_2$ $[M+1]^+$: 749.57683; found: 749.57661.

1,3-Bis(2,7-dicyclooctylnaphthalen-1-yl)imidazolium chloride. Paraformaldehyde (80 mg, 2.67 mmol) was added to 2.0 ml of a 4 N solution of HCl in dioxane (8.0 mmol). The mixture was stirred and gently warmed until complete dissolution of the solid. In another flask, *N*,*N*'-Bis(2,7-dicyclooctylnaphthalene)ethylenediimine (1.0 g, 1.34 mmol) was gently warmed in 4 ml THF until it completely disolved. At room



temperature, the paraformaldehyde solution was added dropwise into the diimine solution at 60 °C slowly. The mixture was stirred at the same temperature overnight and the precipitate was filtered and then disolved in 10 ml of CH_2Cl_2. 200 ml of ether was added into this solution to get the precipitate again. The precipitate was collected and dry under vacuum. The title compound was obtained as a white solid (490 mg, 46% yield). From NMR analysis two isomers existed in the ratio of 92:8. (Due to overlap of most of the signals of minor and major isomer, only the one related to the major will be presented). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.38 (s, 1H), 8.49 (s, 2H), 8.00 (d, J = 8.6 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 7.54-7.48 (m, 4H), 6.89 (s, 2H), 2.78 (br, 2H), 2.51-2.47 (m, 2H), 1.95-1.48 (m, 56H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 152.04, 144.25, 131.98, 131.29, 129.61, 129.23, 128.49, 126.96, 125.88, 124.25, 117.48, 46.84, 41.89, 35.14, 34.98, 33.29, 33.21, 28.19, 27.76, 27.31, 26.84, 26.28, 26.21, 26.10, 25.92, 25.78, 24.21. HRMS (ESI): *m/z* : calcd for $C_{55}H_{73}N_2$ [M-Cl]$^+$: 761.57683; found: 761.57696.



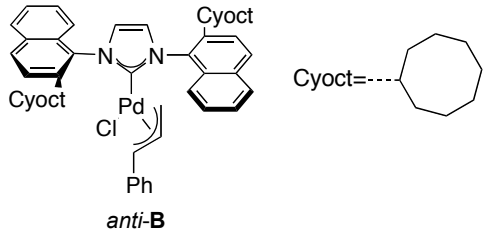
anti-**A** *syn*-**A**

*anti-(2)-(*SICyoctNap)Pd(cin)Cl *syn-(2)-(*SICyoctNap)Pd(cin)Cl

Chloro[(1,2,3-n)-3-phenyl-2-propenyl][1,3-bis(2-cyclooctylnaphthalen-1-yl)-imidazolin-2-ylidene] palladium(II) (*anti*-A and ***syn*-A).** 1,3-Bis(2-cyclooctylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (750 mg, 1.19 mmol), KO*t*Bu (133 mg, 1.19 mmol) and [Pd(cinnamyl)Cl]$_2$ (308 mg, 0.60 mmol) were mixed together in a round flask in the glovebox. Dry THF (45 mL) was added and the mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was separated by flash chromatography on siliga gel (n-hexane :EtOAc 1:7→1:4) to afford two atropisomers (812 mg, 85%). Elemental analysis (%, based on the *rac*-isomer): calcd for $C_{48}H_{55}ClN_2Pd \cdot 2EtOAc$: C, 68.77; H, 7.32; N, 2.86. Found: C, 70.23; H, 6.99; N, 2.35. HRMS (ESI): *m/z* : calcd for $C_{48}H_{55}N_2Pd$ [M-Cl]$^+$: 765.34115; found: 765.34116.

Data for *anti*-**A** are as follows (760 mg, 80% yield): ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.07 (br, 2H), 7.88-7.84 (m, 4H), 7.54-7.24 (m, 6H), 6.94 (s, 3H), 6.66 (br, 2H), 4.61-4.20 (m, 5H), 3.89 (br, 1H), 3.64 (br, 2H), 3.02-2.83 (m, 1H), 2.38-2.25 (m, 2H), 1.95-1.74 (m, 27H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz):213.79, 146.34, 146.12, 138.46, 138.34, 137.22, 136.36, 133.00, 132.90, 132.78, 132.60, 132.48, 131.11, 130.93, 129.49, 129.30, 128.76, 128.24, 128.19, 128.15, 128.08, 127.90, 127.70, 127.68, 127.64, 127.41, 127.34, 126.74, 126.62, 126.51, 126.38, 125.94, 125.86, 125.76, 125.02, 124.96, 124.832, 109.91, 109.57, 106.18, 106.13, 91.45, 90.90. 89.28, 88.02, 82.05, 59.74, 54.07, 53.93, 53.78, 51.33, 50.56, 48.92, 48.32, 38.89, 38.35, 37.82, 37.76, 36.99, 35.93, 34.91, 34.27, 28.3, 28.03, 27.49. 27.15, 26.90, 26.86, 26.76, 26.63, 26.58, 26.48, 26.17. 25.83.

Data for *syn*-**A** are as follows (52 mg, 5% yield): ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.06 (br, 2H), 7.94-7.86 (m, 4H), 7.70-7.68 (m, 1H), 7.60-7.55 (m, 4H), 7.48-7.45 (m, 1H), 6.97 (s, 3H), 6.70 (br, 2H), 4.29 (br, 4H), 4.16-4.14 (m, 1H), 3.72 (d, J = 12.2 Hz, 1H), 3.57 (br, 1H), 3.46 (br, 1H), 2.65-2.58 (m, 2H), 2.31 (br, 1H), 1.89-1.65 (m, 22H), 1.33-1.24 (m, 3H), 0.88-0.85 (m, 2H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 215.11, 147.97, 147.47, 138.79, 133.21, 132.98, 132.46, 132.35, 131.02, 130.81, 129.43, 129.17, 128.94, 128.84, 128.17, 127.91, 127.57, 127.28, 126.82, 126.60, 126.45, 126.31, 125.71, 125.51, 123.63, 123.26, 109.87, 86.83, 54.31, 53.50, 50.50, 39.36, 38.96, 36.48, 36.09, 34.42, 34.08, 33.69, 27.76, 26.85, 26.70, 26.61, 26.56, 22.63, 14.36.

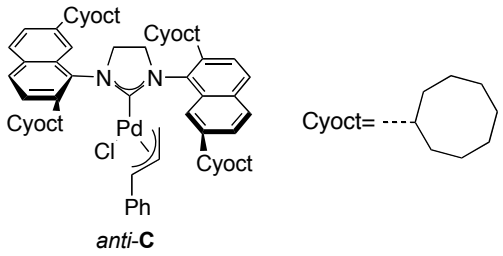


anti-**B**

anti-(2)-(ICyoctNap)Pd(cin)Cl

Chloro[(1,2,3-n)-3-phenyl-2-propenyl][1,3-bis(2-cyclooctylnaphthalen-1-yl)-imidazol-2-ylidene] palladium(II) (*anti*-B). 1,3-Bis(2-cyclooctylnaphthalen-1-yl)imidazolium chloride (200 mg, 0.34 mmol), KO*t*Bu (38 mg, 0.34 mmol) and dry THF (20 ml) were stirred for 5 h in a round flask in the glovebox. Then [Pd(cinnamyl)Cl]$_2$ (44 mg, 0.085 mmol) was added and the mixture was stirred at room temperature for 20 h. The solvent was removed in vacuo, and the residue was separated by flash chromatography on siliga gel (n-hexane:EtOAc 5:1) to afford only

one atropisomer (140 mg, 50%). Elemental analysis (%): calcd for $C_{48}H_{53}ClN_2Pd$: C, 72.08; H, 6.68; N, 3.50. Found: C, 72.16; H, 6.72; N, 3.42. HRMS (ESI): *m/z* : calcd for $C_{48}H_{53}N_2Pd$ [M-Cl]$^+$: 763.32550; found: 763.32555. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.97-7.94 (m, 2H), 7.86 (br, 2H), 7.57-7.45 (m, 8H), 7.36 (s, 2H), 6.97 (s, 3H), 6.76 (s, 2H), 4.69-4.63 (m, 0.5H), 4.41 (br, 0.5H), 4.00-3.93 (m, 1H), 3.21-3.15 (m, 2H), 2.74 (br, 0.5H), 2.63 (bt, 0.5H), 1.99 (s, 1H), 1.96 (s, 1H), 1.79-1.60 (m, 27H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 186.33, 186.05, 185.45, 145.53, 145.34, 138.58, 138.36, 136.48, 132.42, 132.38, 132.22, 132.20, 132.19, 132.15, 131.43, 131.03, 130.24, 128.27, 128.13, 127.87, 127.76, 127.51, 127.41, 127.04, 126.19, 125.36, 125.29, 124.92, 124.73, 124.61, 109.43, 109.02, 105.70, 90.04, 89.07, 87.38, 51.33, 48.71, 47.73, 38.73, 38.34,37.13, 36.17, 34.53, 34.31, 33.82, 27.31, 27.19, 27.13, 26.73, 26.65, 26.56, 26.34, 26.29, 26.15, 25.98.

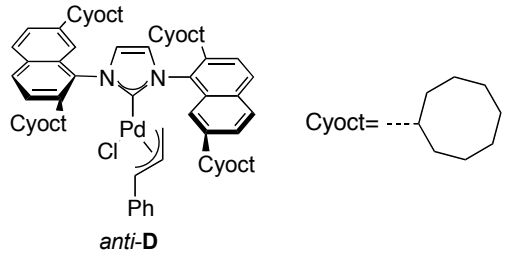


anti-**C**

*anti-(2,7)-(*SICyoctNap)Pd(cin)Cl

Chloro[(1,2,3-n)-3-phenyl-2-propenyl][1,3-bis(2,7-dicyclooctylnaphthalen-1-yl)-imidazolin-2-ylidene] palladium(II) (*anti*-C). 1,3-bis(2,7-dicyclooctylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (388 mg, 0.46 mmol), KO*t*Bu (51 mg, 0.46 mmol) and [Pd(cinnamyl)Cl]$_2$ (120 mg, 0.23 mmol) were mixed together in a round flask in the glovebox. Dry THF (40 mL) was added and the mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was separated by flash chromatography on siliga gel (n-hexane:EtOAc 5:1) to afford one atropisomers (400 mg, 86%). Elemental analysis (%): calcd for $C_{64}H_{83}ClN_2Pd$: C, 75.20; H, 8.18; N, 2.74. Found: C, 75.43; H, 8.15; N, 2.59. HRMS (ESI): *m/z* : calcd for $C_{64}H_{83}N_2Pd$ [M-Cl]$^+$: 985.56068; found: 985.56063. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.84-7.72 (m, 6H), 7.52-7.47 (m, 2H), 7.41-7.37 (m, 2H), 6.99-6.98 (m, 3H), 6.85-6.78 (m, 2H), 4.78-3.85 (m, 6H), 3.52 (br, 2H), 3.01 (br, 2H), 2.76-2.22 (m, 2H), 1.95-0.83 (m, 56H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 212.89, 212.55, 211.33, 149.04, 138.72, 138.47, 138.21, 136.58, 132.71, 132.50, 132.38, 131.62, 131.55, 131.45, 131.36, 131.32, 130.97, 129.01, 128.89, 128.81, 128.57, 128.39, 128.22,

128.16, 128.02, 127.97, 127.64, 127.34, 127.25, 126.44, 125.83, 125.65, 125.56, 125.40, 124.94, 121.46, 109.83, 109.43, 109.13, 106.06, 90.38, 88.01, 87.53, 53.87, 53.63, 48.24, 47.68, 46.43, 46.23, 45.80, 40.90, 40.75, 39.80, 39.66, 36.12, 35.73, 35.14, 35.02, 34.94, 34.70, 33.49, 33.02, 29.98, 29.94, 29.07, 28.73, 28.54, 28.16, 28.02, 27.89, 27.76, 27.58, 27.53, 27.47, 27.37, 27.28, 27.20, 27.15, 26.90, 26.70, 26.62, 26.53, 26.48, 26.42, 26.35, 26.32, 26.19, 26.07, 25.89, 25.07, 24.85, 22.97, 14.39.



anti-**D**

*syn-(2,7)-(*lCyoctNap)Pd(cin)Cl

Chloro[(1,2,3-n)-3-phenyl-2-propenyl][1,3-bis(2,7-dicyclooctylnaphthalen-1-yl)-imidazol-2-ylidene] palladium(II) (*anti*-D). 1,3-Bis(2,7-dicyclooctylnaphthalen-1-yl)imidazolium chloride (288 mg, 0.36 mmol), KO*t*Bu (40 mg, 0.36 mmol) and dry THF (20 ml) were stirred for 20 min in a round flask in the glovebox. Then $[Pd(cinnamyl)Cl]_2$ (93 mg, 0.18 mmol) was added and the mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was separated by flash chromatography on siliga gel (n-hexane:EtOAc 5:1) to afford only one atropisomer (200 mg, 56%). Elemental analysis (%): calcd for $C_{64}H_{81}ClN_2Pd$: C, 75.35; H, 8.00; N, 2.75. Found: C, 75.52; H, 8.07; N, 2.71. HRMS (ESI): *m/z* : calcd for $C_{64}H_{81}N_2Pd$ $[M\text{-}Cl]^+$: 983.54345; found: 983.54573. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.91-7.79 (m, 4H), 7.57-7.28 (m, 8H), 7.00-6.86 (m, 5H), 4.75-3.94 (m, 1H), 3.11 (br, 2H), 2.87 (br, 2H), 2.67-2.55 (m, 1H), 2.34-1.12 (m, 58H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 186.18, 185.97, 185.23, 149.40, 149.16, 149.14, 148.42, 148.31, 145.88, 145.82, 144.54, 138.81, 138.58, 138.33, 136.60, 134.74, 134.62, 132.26, 132.18, 132.08, 131.96, 131.44, 131.29, 131.17, 131.09, 131.03, 130.99, 130.93, 130.89, 130.80, 129.70, 129.44, 128.63, 128.48, 128.37, 128.26, 128.24, 128.17, 128.06, 127.99, 127.68, 127.36, 127.27, 126.38, 125.94, 125.86, 125.83, 125.81, 125.64, 125.19, 124.87, 124.79, 124.46, 121.34, 121.20, 120.41, 120.15, 109.41, 109.04, 108.63, 105.49, 89.46, 88.97, 87.20, 86.88, 68.24, 60.66, 48.06, 47.61, 46.57, 46.41, 46.26, 46.12, 45.68, 41.14, 40.48, 40.26, 39.52, 39.48, 35.78, 35.00, 34.93, 34.45, 34.03, 33.92, 33.76, 33.59, 33.56, 32.98, 32.36, 32.15, 31.86, 29.30, 28.60,

28.25, 28.02, 27.95, 27.66, 27.64, 27.58, 27.47, 27.38, 27.33, 27.15, 27.12, 26.98, 26.94, 26.60, 26.56, 26.40, 26.34, 26.30, 26.25, 26.21, 26.16, 26.08, 26.02, 25.89, 25.88, 25.84, 25.45, 25.12, 24.77, 22.97, 22.93, 14.41.

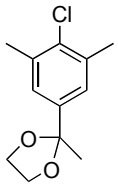
2-Methyl-1-naphthylboronicacid. 1-Bromo-2-methylnaphthalene (2.81 g, 12.7 mmol), magnesium (338 mg, 13.9 mmol) and one crystal of I_2 were refluxed in 20 ml THF for 2 h. Upon cooling to room temperature, the generated grinard reagent was added dropwise into the solution of $B(OMe)_3$ (2.2 ml, 19.1 mmol) in 8 ml THF under 0 °C. The mixture was stirred for another 1 h under 0 °C and then overnight at room temperature. The reaction was quenched with 5 ml water and the whole mixture was concentrated by evaporation. To the residue was added 40 ml HCl aqueous solution (1 mol/L) and the mixture was stirred for 30 min to get the precipitate. The yellow precipitate was stirred in 50 ml n-hexane for 2 h. After filtration, the title compound was obtained as a white solid (1.60 g, 68% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.80 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.45 (td, J = 6.9, 1.3 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 4.78 (s, 2H), 2.56 (s, 3H).

1-Chloro-4-methoxy-2,6-dimethylbenzene. 4-Chloro-3,5-dimethylphenol (1.88 g, 12.0 mmol) was treated with anhydrous K_2CO_3 (5.0 g, 36.0 mmol) and iodomethane (6.8 g, 48.0 mmol) in refluxing acetone for 3 h. To the residue after evaporation was added 50 ml water and 50 ml CH_2Cl_2. The organic phase was washed with 30 ml NaOH solution (2 mol/L) and then with water. After drying over anhydrous $MgSO_4$, the solvent was removed in vacuo and the title compound was obtained as a colorless oil (1.72 g, 84% yield). %).^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.63 (s, 2H), 3.75 (s, 3H), 2.35 (s, 6H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 157.68, 137.32, 126.46, 114.16, 55.57, 21.19.

4-Chloro-3,5-dimethylacetophenone. In a 100 ml schlenk flask was charged with dry chloroform (30 ml), 2-chloro-1,3-dimethylbenzene (7 g, 50 mmol). The mixture was cooled to 0 °C and then a pre-mixed solution of aluminum trichloride (6.3 g, 47.5 mmol) and acetyl chloride (3.2 ml, 45 mmol) was added to this chloroform solution in 1h via addition funnel. The reaction was gradually warmed to room temperature and stirred for another 1h

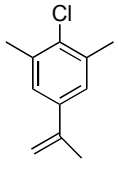
and then quenched with ice (50 g). The aqueous was extracted with 50 ml chloroform and the combined organic phase was washed with 50 ml saturated K_2CO_3 until slightly basic. The organic layer was further washed with water (50 ml) and brine (50 ml) and then dried over anhydrous $MgSO_4$. After rotary evaporation, the mixture was purified with flash chromatography on silica gel (n-hexane:EtOAc 10:1) to get the title compound as a colorless solid (5.0 g, 61% yield). HRMS (EI): *m/z* : calcd for $C_{10}H_{11}ClO\,[M]^+$: 182.0498; found: 182.0498. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.64 (s, 2H), 2.55 (s, 3H), 2.41 (s, 6H). ^{13}C {^1H} NMR ($CDCl_3$, 100 MHz): 197.82, 140.27, 136.98, 135.10, 128.47, 26.86, 21.09.

2-(4-chloro-3,5-dimethylphenyl)-2-methyl-1,3-Dioxolane. To a solution of 4-



Chloro-3,5-dimethylacetophenone (1.0 g, 5.5 mmol) in toluene (10 ml) was added ethylene glycol (1.02 g, 16.5 mmol) and a catalytic amount of *p*-toluene sulfonic acid. The mixture was refluxed for 12h with a Dean-Stark trap. Upon cooling to room temperature, the solution was extracted with 50 ml EtOAc. The organic phase was washed with water (50 ml) and brine (50 ml) and then dried over anhydrous $MgSO_4$. After removing the solvent by evaporation, the residue was purified by flash chromotagraphy on siliga gel (n-hexane:CH_2Cl_2 2:1) to get the product as a colorless oil (686 mg, 55% yield). HRMS (ESI): *m/z* : calcd for $C_{10}H_{11}ClNaO\,[M\text{-}C_2H_4O\text{+}Na]^+$: 205.03906; found: 205.03901. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.18 (s, 2H), 4.02-3.99 (m, 2H), 3.78-3.74 (m, 2H), 2.36 (s, 6H), 1.61 (s, 3H). ^{13}C {^1H} NMR ($CDCl_3$, 100 MHz): 141.38, 136.31, 134.35, 108.75, 64.74, 27.88, 21.07.

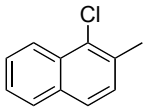
1,3-Dimethyl-2-chloro-5-(1-methylethenyl)-benzene. To a suspension of



methyltriphenylphosphonium bromide (1.17 g, 3.27 mmol) in 30 ml THF was added NaO*t*Bu as a solid in small portions. The obtained bright yellow mixture was stirred for 1 h at room temperature under N_2 and then cooled to -78 °C. To this mixture 4-chloro-3,5-dimethylacetophenone solution in 5 ml THF was added. The reaction was allowed to gradually warm to room temperature before quenching with water. The organic layer was washed with water (30 ml), brine (30 ml) and then dried over anhydrous $MgSO_4$ and concentrated in vacuo. To the residue n-hexane (20 ml) was added and the immediate formation of the precipitate was observed. After filtration, the solid was washed with 20 ml n-

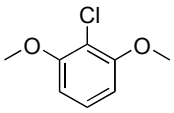
hexane and the combined n-hexane solution was dried. The crude product was purified by flash chromatography on siliga gel (n-hexane) to afford the title compound as a colorless oil (392 mg, 80% yield). HRMS (ESI): *m/z* : calcd for $C_{11}H_{13}Cl$ $[M]^+$: 180.0706; found: 180.0706. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.16 (s, 2H), 5.31 (s, 1H), 5.05 (s, 1H), 2.37 (s, 6H), 2.11 (s, 3H). ^{13}C {^1H} NMR ($CDCl_3$, 100 MHz): 142.86, 139.37, 136.12, 134.00, 125.89, 112.79, 22.12, 21.10.

1-Chloro-2-methylnaphthalene. The suspension of 1-bromo-2-methylnaphthalene

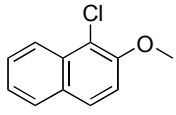


(2.0 g, 9.0 mmol) and CuCl (960 mg, 9.7 mmol) in 30 ml DMF was refluxed for 7 h. Upon cooling to room temperature, the mixture was filtered through a plug silica gel with n-hexane as eluent. After evaporation of the solvent, the residue was purified by flash chromatography on siliga gel(n-hexane) to afford the title compound as a colorless oil (1.34 g, 84% yield). HRMS (EI): *m/z* : calcd for $C_{11}H_9Cl$ $[M]^+$: 176.0393; found: 176.0394. ^1H NMR ($CDCl_3$, 400 MHz): 8.29 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.56 (td, *J* = 8.4,1.3 Hz, 1H), 7.46 (td, *J* = 8.0,1.0 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 2.58 (s, 3H). ^{13}C {^1H} NMR ($CDCl_3$, 100 MHz):133.73, 133.32, 131.45, 130.94, 128.98, 128.25, 127.25, 126.71, 125.89, 124.42, 21.09.

1-Chloro-2,6-dimethoxybenzene. The suspension of 1-bromo-2,6-



dimethoxybenzene (500 mg, 2.3 mmol) and CuCl (250 mg, 2.5 mmol) in 15 ml DMF was refluxed overnight. Upon cooling to room temperature, the mixture was filtered through a plug silica gel with n-hexane as eluent. After evaporation of the solvent, the residue was purified by flash chromatography on siliga gel (n-hexane/ether 10:1) to afford the title compound as a white solid (370 mg, 93% yield). HRMS (EI): *m/z* : calcd for $C_8H_9O_2Cl$ $[M]^+$: 172.0291; found: 172.0291. ^1H NMR ($CDCl_3$, 400 MHz): 7.16 (t, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 2H), 3.88 (s, 6H). ^{13}C {^1H} NMR ($CDCl_3$, 100 MHz): 156.58, 127.42, 105.01, 105.00, 56.64.

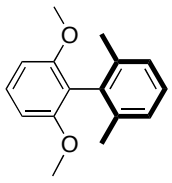


1-Chloro-2-methoxynaphthalene. The suspension of 1-bromo-2-methoxynaphthalene (1.0 g, 4.2 mmol) and CuCl (459 mg, 4.6 mmol) in 25 ml DMF was refluxed overnight. Upon cooling to room temperature, the mixture was filtered through a plug silica gel with n-hexane as

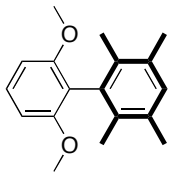
eluent. After evaporation of the solvent, the residue was purified by flash chromatography on siliga gel (n-hexane/ether 10:1) to afford the title compound as a white solid (370 mg, 93% yield). HRMS (EI): *m/z* : calcd for $C_{11}H_9OCl$ $[M]^+$: 192.0342; found: 192.0340. ^1H NMR ($CDCl_3$, 400 MHz): 8.20 (d, *J* = 8.6 Hz, 1H), 7.77 (t, *J* = 8.6 Hz, 2H), 7.55 (t, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H). ^{13}C {^1H} NMR ($CDCl_3$, 100 MHz): 152.86, 132.19, 129.83, 128.28, 128.25, 127.74, 124.61, 123.77, 57.29.

2.5.2 General Suzuki-coupling procedure. In the glovebox, a vial (10 mL screw-cap threaded) equipped with a stir-bar was charged with arylhalide (0.40 mmol), boronic acid (0.60 mmol for bromides or 0.80 mmol for chlorides), potassium *tert*-butoxide (112 mg, 1.0 mmol), then the Pd-complex *anti*-**C (**8.2 mg, 0.0080 mmol) and toluene (3.2 ml) were added. The mixture was stirred at room temperature for indicated period of time before being quenched with water (10 ml) outside the golvbox (the reaction mixture turned into a red and homogeneous solution before it completed). Alternatively, if heating was needed, the vial was sealed a Teflon®-lined screw cap and the mixture was stirred at 65 °C for indicated period of time before being quenched with water (10 ml). The mixture was extracted with ethylacetate (15 ml × 2) and the combined organic layers were dried with anhydrous $MgSO_4$, the solvent was removed in vacuo and the residue was purified by flash chromatography.

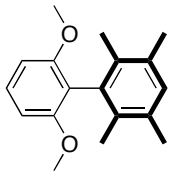
2,6-Dimethoxy-2',6'-dimethylbiphenyl (Table 4, Entry 1): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 12 h at room temperature,93.0 mg (96% yield) of the product was isolated by flash chromatography (n-N-hexane/Ether = 20/1) as a white solid. The spectral data were in accordance with those reported in the literature.[20b]



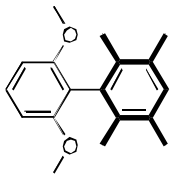
2,6-Dimethoxy-2',3',5',6'-tetramethylbiphenyl (Table 4, Entry 2): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 72 h at room temperature, 86 mg (80% yield) of the product was isolated by flash chromatography (n-Hexane/Ether = 20/1) as a white solid. HRMS (EI): *m/z* : calcd for $C_{18}H_{22}O_2$ $[M]^+$: 270.1620; found: 270.1622. ^1H NMR ($CDCl_3$, 500 MHz): 7.30 (t, *J* = 8.3 Hz, 1H),



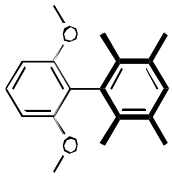
6.97 (s, 1H), 6.65 (d, J = 8.3 Hz, 1H), 3.70 (s, 6H), 2.26 (s, 6H), 1.86 (s, 6H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 157.92, 134.05, 133.12, 133.03, 131.14, 128.58, 119.20, 104.18, 56.07, 20.59, 16.67.



2,6-Dimethoxy-2',3',5',6'-tetramethylbiphenyl (Table 4, Entry 3): The general Suzuki coupling procedure was followed, using *anti*-**C** (4.1 mg, 0.004 mmol). After 2 h at 65 °C, 104 mg (96% yield) of the product was isolated. The spectral data were identical with those in Table 4, Entry 2.

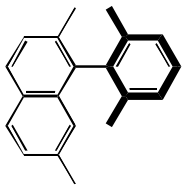


2,6-Dimethoxy-2',3',5',6'-tetramethylbiphenyl (Table 4, Entry 4): The general Suzuki coupling procedure was followed, using *anti*-**C** (2.0 mg, 0.002 mmol) and 2 ml Toluene. After 3 h at 65 °C, 99 mg (92% yield) of the product was isolated. The spectral data were identical with those in Table 2, Entry 2.



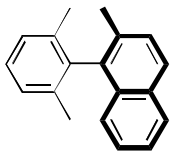
2,6-Dimethoxy-2',3',5',6'-tetramethylbiphenyl (Table 4, Entry 5): The general Suzuki coupling procedure was followed, using *anti*-**C** (0.82 mg, 0.0008 mmol) and 2 ml Toluene. After 12 h at 65 °C, 105 mg (97% yield) of the product was isolated. The spectral data were identical with those in Table 4, Entry 2.

1-(2´,6´-dimethylphenyl)-2,7-dimethylnaphthalene (Table 4, Entry 6): The

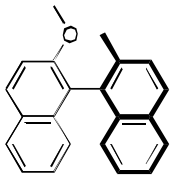


general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 15 h at room temperature, 96 mg (92% yield) of the product was isolated by flash chromatography (n-Hexane) as a colorless oil. HRMS (EI): *m/z* : calcd for $C_{20}H_{20}$ $[M]^+$: 260.1565; found: 260.1567. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.79-7.76 (m, 2H), 7.40 (d, J = 8.4 Hz, 1H), 7.32-7.26 (m, 4H), 7.00 (s, 1H), 2.38 (s, 3H), 2.12 (s, 3H), 1.88 (s, 6H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 139.04, 136.98, 136.17, 135.96, 133.15, 132.40. 130.78, 128.12, 128.02, 127.71, 127.39, 127.02, 124.10, 22.22, 20.21, 20.12.

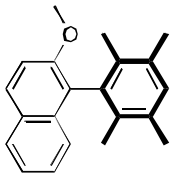
2-Methyl-1-(2′,6′-dimethylphenyl)-naphthalene (Table 4, Entry 7): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 12 h at room temperature, 84 mg (85% yield) of the product was isolated by flash chromatography (n-hexane) as a colorless oil. The spectral data were in accordance with those reported in the literature.[18a]



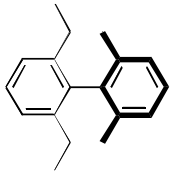
2-methoxy-2'-methyl-1,1'-binaphthyl (Table 4, Entry 8): The general Suzuki coupling procedure was followed, using *anti*-**C** (4.1 mg, 0.0040 mmol). After 16 h at room temperature, 113 mg (95% yield) of the product was isolated by flash chromatography (n-hexane:ether 20:1) as a white solid. The spectral data were in accordance with those reported in the literature.[30]

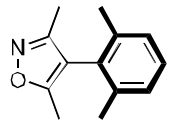


2-Methoxy-1-(2′,3′,5′,6′-tetramethylphenyl)-naphthalene (Table 4, Entry 9): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 10 h at room temperature, 106 mg (91% yield) of the product was isolated by flash chromatography (n-hexane: CH_2Cl_2 10:1) as a white solid. HRMS (EI): *m/z* : calcd for $C_{21}H_{22}O$ $[M]^+$: 290.1671; found: 290.1671. ^1H NMR ($CDCl_3$, 400 MHz): 7.91 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.37-7.28 (m, 2H), 7.16 (d, J = 8.2 Hz, 1H), 7.09 (s, 1H), 3.86 (s, 3H), 2.33 (s, 6H), 1.78 (s, 6H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 100 MHz): 153.85, 135.84, 133.56, 133.52, 133.35, 131.11, 129.37, 128.86, 128.14, 126.58, 125.14, 124.94, 123.71, 113.85, 56.68, 20.54, 16.71.



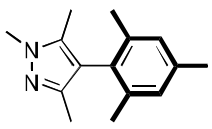
2,6,-Diethyl-2',6',-dimethylbiphenyl (Table 4, Entry 10): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 18 h at room temperature, 64 mg (67% yield) of the product was isolated by flash chromatography (n-hexane) as a colorless oil. The spectral data were in accordance with those reported in the literature.[18a]



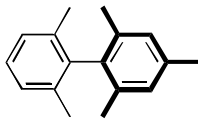


4-(2´,6´-dimethylphenyl)-3,5-dimethylisoxazole (Table 4, Entry 11): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 20 h at room temperature, 56 mg (70% yield) of the product was isolated by flash chromatography (n-hexane:EtOAc 20:1) as a white solid. The spectral data were in accordance with those reported in the literature.[16a]

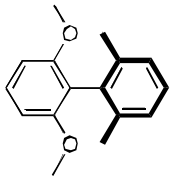
4-mesityl-1,3,5-trimethyl-1*H*-pyrazoleThe (Table 4, Entry 12): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 20 h at room temperature, 80 mg (88% yield) of the product was isolated by flash chromatography (n-hexane:EtOAc 3:2) as a colorless oil. The spectral data were in accordance with those reported in the literature.[31]



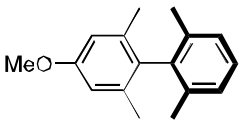
2,2',4,6,6'-Pentamethylbiphenyl (Table 5, entry 1): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 8 h at room temperature, 70 mg (78% yield) of the product was isolated by flash chromatography (n-hexane) as a colorless oil. The spectral data were in accordance with those reported in the literature.[18a]

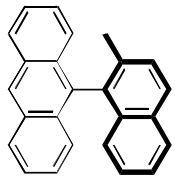


2,6-Dimethoxy-2',6'-dimethylbiphenyl (Table 5, Entry 2): The general Suzuki coupling procedure was followed, using *anti*-**C** (4.1 mg, 0.0040 mmol). After 8 h at 65 °C, 78 mg (80% yield) of the product was isolated by flash chromatography (n-hexane:ether 20/1) as a white solid. The spectral data were identical with those in Table 4, Entry 1.



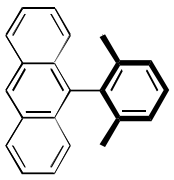
4-Methoxy-2,2',6,6'-tetramethyl-biphenyl (Table 5, entry 3): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 2 h at 65 °C, 69 mg (72% yield) of the product was isolated by flash chromatography (n-hexane:EtOAc 30:1) as a colorless oil. The spectral data were in accordance with those reported in the literature.[18a]



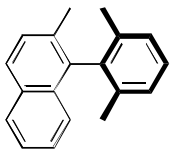


9-(2´-methylnaphthalen-1-yl)anthracene (Table 5, entry 4): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 20 h at room temperature, 117 mg (92% yield) of the product was isolated by flash chromatography (n-hexane) as a white solid. The spectral data were in accordance with those reported in the literature.[19]

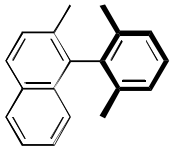
9-(2´,6´-Dimethylphenyl)anthracene (Table 5, entry 6) : The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 20 h at room temperature, 97 mg (86% yield) of the product was isolated by flash chromatography (n-hexane) as a white solid. The spectral data were in accordance with those reported in the literature.[16a]



2-Methyl-1-(2´,6´-dimethylphenyl)-naphthalene (Table 5, Entry 7): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 8 h at room temperature, 88 mg (89% yield) of the product was isolated by flash chromatography (n-hexane) as a colorless oil. The spectral data were identical with Table 4, Entry 7.

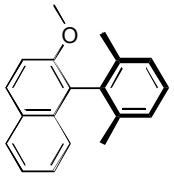


2-Methyl-1-(2´,6´-dimethylphenyl)-naphthalene (Table 5, Entry 8): The general Suzuki coupling procedure was followed, using *anti*-**C** (2.0 mg, 0.002 mmol) and 2 ml of Toluene. After 1.5 h 65 °C, 84 mg (85% yield) of the product was isolated by flash chromatography (n-hexane) as a colorless oil. The spectral data were identical with Table 4, Entry 7.



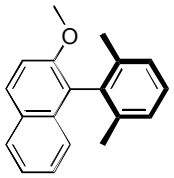
2,2´-dimethyl-1,1´-binaphthalene (Table 5, Entry 9): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 16 h at room temperature, 93 mg (82% yield) of the product was isolated by flash chromatography (n-hexane) as a colorless oil. The spectral data were in accordance with those reported in the literature.[31]

1-(2′,6′-dimethylphenyl)-2-methoxynaphthalene (Table 5, Entry 10): The general Suzuki coupling procedure was followed, using *anti*-**C** (4.1 mg, 0.0040 mmol). After 10 h at room temperature, 95 mg (90% yield) of the product was isolated by flash chromatography (n-hexane:EtOAc 30:1) as a white solid. The spectral data were in accordance with those reported in the literature.[16a]

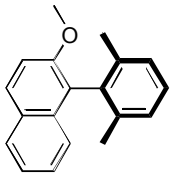


1-(2′,6′-dimethylphenyl)-2-methoxynaphthalene (Table 5, Entry 11): The general Suzuki coupling procedure was followed, using *anti*-**C** (4.1 mg, 0.0040 mmol). After 10 h at 65 °C, 96 mg (91% yield) of the product was isolated by flash chromatography (n-hexane:EtOAc 30:1) as a white solid. The spectral data were indentical with Table 5, Entry 10.

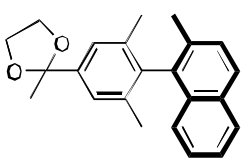
1-(2′,6′-dimethylphenyl)-2-methoxynaphthalene (Table 5, Entry 12): The general Suzuki coupling procedure was followed, using *anti*-**C** (2.0 mg, 0.0020 mmol, from stock solution) and 2 ml of toluene. After 1.5 h at 65 °C, 92 mg (88% yield) of the product was isolated by flash chromatography (n-hexane:EtOAc 30:1) as a white solid. The spectral data were indentical with Table 5, Entry 10.



1-(2′,6′-dimethylphenyl)-2-methoxynaphthalene (Table 5, Entry 13): The general Suzuki coupling procedure was followed, using *anti*-**C** (0.8 mg, 0.00080 mmol, from stock solution) and 2 ml of toluene. After 7 h at 65 °C, 84 mg (80% yield) of the product was isolated by flash chromatography (n-hexane:EtOAc 30:1) as a white solid. The spectral data were indentical with Table 5, Entry 10.

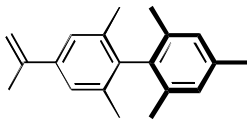


2-[3,5-Dimethyl-4-(2-methyl-naphathalen-1-yl)phenyl]-2-methyl-[1,3]dioxolane (Table 5, entry 14): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 20 h at room temperature, 104 mg (78% yield) of the product was

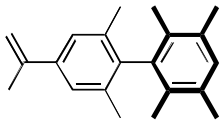


isolated by flash chromatography (n-hexane:EtOAc 5:1) as a colorless oil. The spectral data were in accordance with those reported in the literature.[18a]

2,2′,4′,6,6′-pentmethyl-4-(1-methylethenyl)biphenyl (Table 5, Entry 15): The

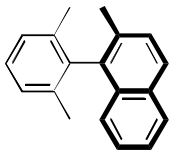


general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 20 h at room temperature, 75 mg (71% yield) of the product was isolated by flash chromatography (n-hexane) as a colorless solid. HRMS (EI): *m/z* : calcd for $C_{20}H_{24}$ $[M]^+$: 264.1878; found: 264.1874. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.22 (s, 2H), 6.93 (s, 2H), 5.41 (s, 1H), 5.06 (s, 1H), 2.32 (s, 3H), 2.17 (s, 3H), 1.90 (s, 6H), 1.86 (s, 6H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 143.22, 139.41, 139.25, 136.83, 136.17, 135.53, 135.34, 128.23, 124.58, 111.53, 21.85, 21.12, 20.06, 19.79.



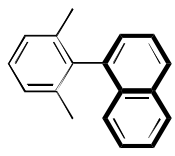
2,2′,3′,5′ ,6,6′-hexamethyl-4-(1-methylethenyl)biphenyl (Table 5, Entry 16): The general Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 24 h at room temperature, 80 mg (72% yield) of the product was isolated by flash chromatography (n-hexane) as a white solid. HRMS (EI): *m/z* : calcd for $C_{21}H_{26}$ $[M]^+$: 278.2035; found: 278.2034. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.24 (s, 2H), 6.97 (s, 1H), 5.43 (s, 1H), 5.07 (s, 1H), 2.26 (s, 6H), 2.19 (s, 3H), 1.88 (s, 6H), 1.78 (s, 6H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 143.52, 141.00, 140.04, 139.35, 135.89, 133.83, 131.46, 130.35, 124.76, 111.74, 22.13, 20.48, 20.46, 16.21.

2-Methyl-1-(2′,6′-dimethylphenyl)-naphthalene (Table 5, Entry 17): The general



Suzuki coupling procedure was followed, using *anti*-**C** (8.2 mg, 0.0080 mmol). After 12 h at room temperature, 90 mg (91% yield) of the product was isolated by flash chromatography (n-hexane) as a colorless oil. The spectral data were identical with Table 4, Entry 7.

1-(2′,6′-dimethylphenyl)-naphthalene (Table 5, Entry 18): In the glovebox, a vial



(4 mL screw-cap threaded) equipped with a stir-bar was charged with 2,6-dimethylphenylchloride (70 mg, 0.5 mmol), 1-naphthylboronic acid (95 mg, 0.55 mmol), potassium *tert*-butoxide (73 mg, 0.65 mmol), then the Pd-complex *anti*-**C** **(**0.255 mg, 2.50 x 10^{-4} mmol, from the prepared

stock solution) was added. Outside of the glovebox, 0.5 ml of technical grade isopropanol was added. The mixture was stirred at room temperature 15h before being quenched with water (2 ml). The mixture was extracted with MTBE (15 ml × 2) and the combined organic layers were dried with anhydrous $MgSO_4$, the solvent was removed in vacuo and the residue was purified by flash chromatography (n-hexane). 93 mg (80% yield) of the product was isolated as a colorless oil. The spectral data were in accordance with those reported in the literature.[32]

2.6 References and Notes

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Chapter 3

Synthesis of 3-Allyl/Fluoro-3-Aryl Oxindoles via the Direct Enantioselective Catalytic α-Arylation of Amides

Luan, X.; **Wu, L.**; Drinkel. E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912.

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3.1 Abstract

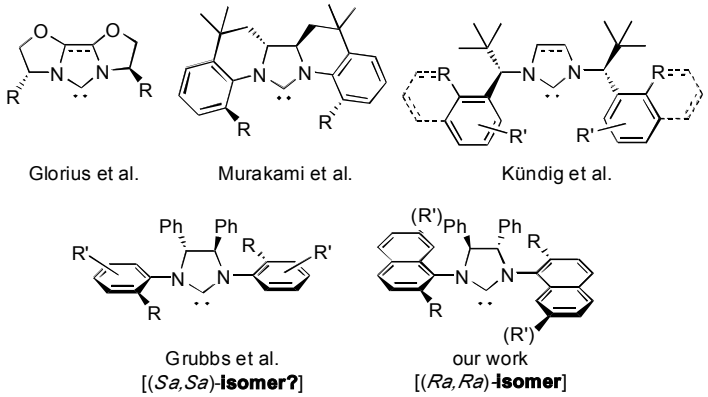
A new NHC•Pd-catalyzed asymmetric α-arylation of amides is reported giving direct access to synthetically valuable, 3-allyl/fluoro oxindoles with quaternary carbon centers. Based on the chiral regime of C_2-symmetric starting diamines, the naphthyl-based chiral NHC ligands were readily prepared. When the 2-positions of the naphthyl side chains were substituted with 3-pentyl groups, three diastereomers were present in the corresponding salt. The palladium complex of one of the isomer (*Ra,Ra*) showed high chemo- and enantioselectivity for the synthesis of chiral 3-allyl oxindoles. When the 2-positions of the naphthyl side chains were substituted with cyclooctyl groups, only one diastereomer exsits in the corresponding salt. The enantiopure NHC ligand was then used to form precatalyst, which was tested in the asymmetric synthesis of 3-aryl-3-fluoro oxindoles. The biologically important oxindoles could be obtained with good yields (up to 94%) and excellent enantioselectivities (up to >99% ee). DFT calculations are offered to rationalize the excellent selectivity.

3.2 Introduction

As part of our ongoing research on employing chiral monodentate *N*-heterocyclic carbene (NHC) ligands for metal-catalyzed asymmetric catalysis, we reported the synthesis of diastereomerically pure palladium complexes incorporating new chiral NHC ligands and their successful application in the Pd-catalyzed intramolecular α-arylation of amides to obtain enantiomerically enriched 3-aryl-3-methyl oxindoles.[1] While elegant as a methodology to obtain chiral quaternary carbon centers, the intramolecular α-arylation at present has the drawback of providing oxindoles that are difficult to functionalize further. We therefore wondered whether 3-allyl-3-aryl oxindoles, previously only accessible via a two-step procedure involving a Pd-catalyzed intramolecular α-arylation followed by an asymmetric Pd-catalyzed allylic alkylation,[2] could be obtained directly. Herein we report the successful achievement of this strategy by using a newly designed NHC ligand.

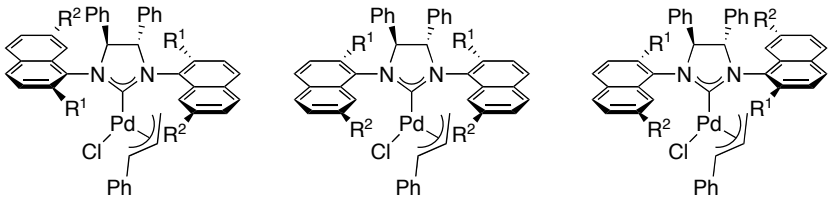
Monodentate N-heterocyclic carbene (NHC) ligands have become ubiquitous in organometallic chemistry and catalysis.[3] Conversely, development of chiral monodentate NHC ligands that induce high selectivity in asymmetric metal catalysis

is still at an early stage with relatively few reports detailing enantioselectivities of 90% ee and higher.[4-8] The main difficulties in designing efficient ligands of this type reside in placing stereocontrol elements at positions near the metal center without affecting the overall reactivity of the catalysts. Scheme 1 shows some of the most promising ligand designs to date and highlights the fact that the inherent flexibility of the N-substituents has to be restricted to afford ligands that efficiently transfer their chiral information. This can be done by fusing these wingtips onto the N-heterocycle, a design motif pioneered by Glorius et al.,[4] and more recently developed further by Murakami et al.[5] Decreasing the rotation of the N-substituents is also key in the successful C_2-symmetric ligand design reported by Kündig et al.,[6] who have been able to show that such ligands can be used very effectively in palladium chemistry. Probably the most versatile ligand system developed so far was first reported by Grubbs et al.,[7,8] and relies on transferring chirality from a chiral *N*-heterocyclic backbone onto unsymmetrically substituted aryl side chains and ultimately onto the metal coordination sphere. While the design permits easy access to the precursor imidazolinium salts, such side chains will in principle create three diastereomers that would have to be separated for optimal use in catalysis. Our own efforts,[9] have indeed highlighted the pivotal role the respective orientation of naphthyl wingtips can have on enantioselectivity and, contrary to what other groups have proposed or found, the best ligands with 2-alkyl-substituted naphthyl side chains position their alkyl substituents directly below the corresponding phenyl group of the backbone [(*Ra,Ra*)-isomer]. Herein we report the successful access to this diastereomer using a newly designed NHC ligand which showed excellent selectivities for synthesis of chiral 3-fluoro-3-aryl oxindoles.



Scheme 1. Examples of chiral, monodentate NHC ligands

3.3 Results and Discussion



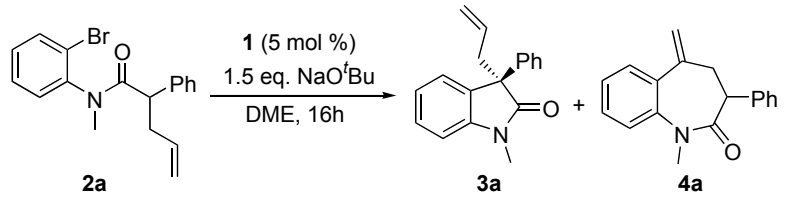
(*Ra*,*Ra*)-**1a** (*Ra*,*Sa*)-**1a** (*Sa*,*Sa*)-**1a**
(*Ra*,*Ra*)-**1b** (*Ra*,*Sa*)-**1b**
(*Ra*,*Ra*)-**1c** (*Ra*,*Sa*)-**1c**
(*Ra*,*Ra*)-**1d** (*Ra*,*Sa*)-**1d** (*Sa*,*Sa*)-**1d**

1a: $R^1 = R^2 = i$Pr **1b**: $R^1 = i$Pr, R^2 = H **1c**: R^1 = Cy, R^2 = H, **1d**:R^1 = 3-pentyl, R^2 = H

Scheme 2. Palladium complexes used as the catalysts

Our investigation commenced by examining the ability of NHC•Pd complexes **1a-c** (Scheme 2), previously developed in our laboratories,[1] to promote the intramolecular α-arylation of the model substrate **2a** (Table 1). At the outset of the study and under the reaction conditions used, it was not clear whether such α-arylations would be preferred over a reaction scenario involving Heck cyclizations giving rise to 7-exo-trig (or 8-endo-trig) products. The catalytic results reported in Table 1 indeed indicate that Heck cyclization is competitive and product **4a** was formed in noticeable amounts (15-20%) with all diastereomers of precatalysts **1a-c**. Trends in enantioselectivity though were immediately apparent. Somewhat surprising was the fact that the diastereomers of catalyst **1a**, which performed best in our previous investigation, gave erratic results with inconsistent absolute configurations of product **3a**. In fact, omitting the R^2-isopropyl group on the naphthyl wingtips of the NHC (precatalysts **2b**) gave more usable results (entries 4, 5). Furthermore, precatalyst **1c** that incorporates a slightly bulkier R^2-cyclohexyl group resulted in better enantioselection (entries 6, 7).

Table 1. Initial screening of Pd-complexes **1a-c**



2a **3a** **4a**

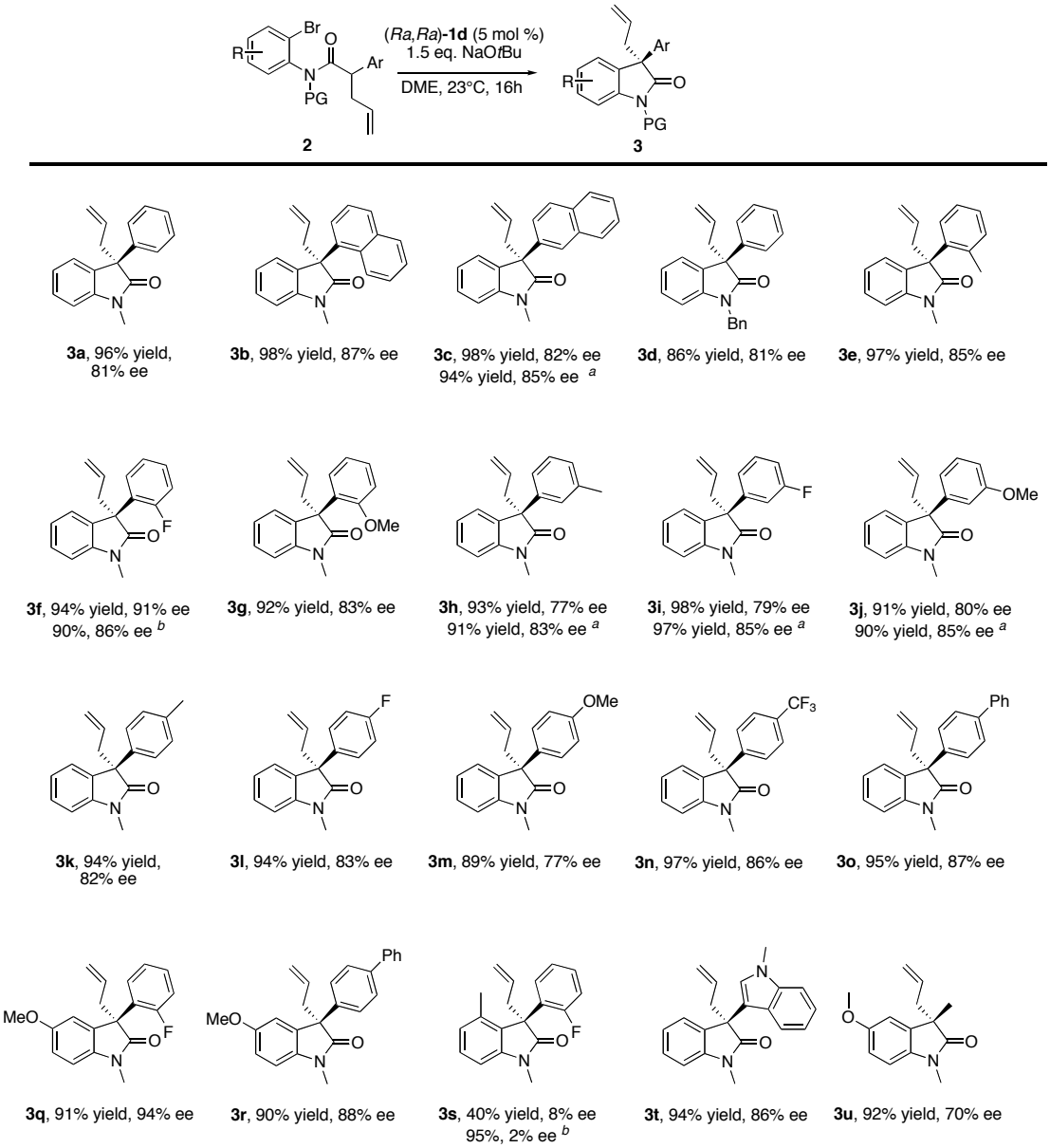
Entry	NHC•Pd	*T* (°C)	Conv [%][a]	**3a**/**4a**[b]	ee [%][c,d]
1	(*Ra*,*Ra*)-**1a**	23	>99	5:1	-24 (*S*)
2	(*Ra*,*Sa*)-**1a**	23	>99	4:1	56 (*R*)
3	(*Sa*,*Sa*)-**1a**	23	>99	5:1	34 (*R*)
4	(*Ra*,*Ra*)-**1b**	50	>99	4:1	39 (*R*)
5	(*Ra*,*Sa*)-**1b**	50	>99	4:1	58 (*R*)
6	(*Ra*,*Ra*)-**1c**	50	>99	6:1	46 (*R*)
7	(*Ra*,*Sa*)-**1c**	50	>99	4:1	66 (*R*)
8	(*Ra*,*Ra*)-**1d**	23	>99	1:0	**81 (*R*)**
9	(*Ra*,*Sa*)-**1d**	23	>99	16:1	**81 (*R*)**
10	(*Sa*,*Sa*)-**1d**	23	>99	1:0	52 (*R*)

[a] Determined by GC-MS. [b] Determined by analysis of ^{1}H NMR spectra of product mixtures prior to purification. [c] Determined by chiral HPLC for **3a**. [d] The absolute configuration of **3a** was assigned according to ref 10.

The tendencies in selectivity observed in Table 1 were subsequently implemented in the design of a modified chiral NHC structure that lacks the R^2 wingtip group and incorporates a bulkier, unstrained 3-pentyl moiety on the 2-position of the naphthyl side chains. We were hoping that the bulkier group would help transfer the chiral information more effectively from the NHC backbone to the side chains, and hence induce higher enantioselectivity. Thus, three separable diastereomers [(*Ra*,*Ra*)-**1d**, (*Ra*,*Sa*)-**1d** and (*Sa*,*Sa*-**1d**)] were prepared relatively easily. These new catalysts were subjected to our standard substrate **2a** (Table 2, entries 8-10). The results were very encouraging and all three diastereomeric precatalysts **1d** proved superior to their congeners **1a-c** both in terms of their higher reactivity (room temperature) and their enhanced selectivity. As an unexpected and very welcome side effect, incorporation of the new NHC ligand also greatly enhanced the chemoselectivity of the transformation with generation of only trace amounts (if any) of Heck byproduct **4a**. As a consequence, treatment of **2a** in the presence of 5 mol % *RaRa*-**1d** gave rise to oxindole **3a** in 96% isolated yield and 81% ee. Because catalyst *RaRa*-**1d** showed the best result in terms of chemoselectivity and enantioselectivity, we examined this complex with other substrates (Scheme 3). Thus, an important number of different amides were synthesized and subjected to the standard reaction conditions [5 mol %

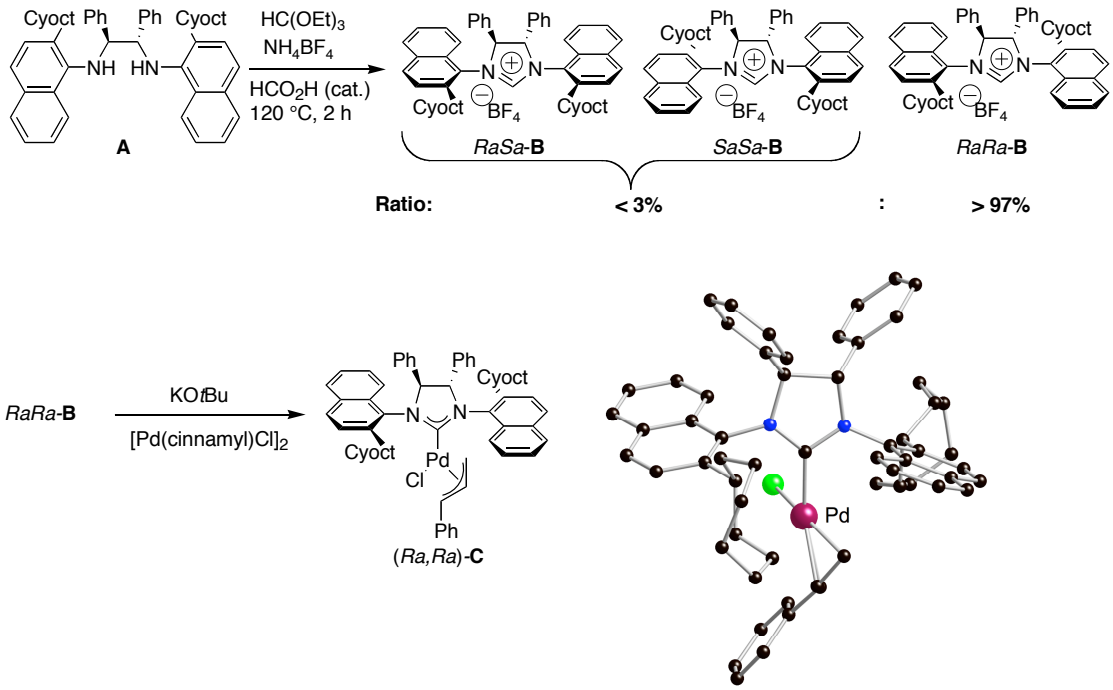
(*Ra,Ra*)-**1d**, 1.5 eq. NaO*t*Bu, DME, 23°C, 16h]. Results in **Scheme 3** show that broad structural variations in the amide system can be accommodated. In nearly all cases, excellent yields, virtually complete chemoselectivities and good-to-excellent enantioselectivities were obtained. For example, *ortho*-substituted aromatic groups are tolerated, and the sterically demanding products were obtained with selectivities of up to 91 % ee (**3f**). The method is compatible with both electron-rich and electron-poor aromatic groups, and *ortho*-, *meta-,* as well as *para*-positions could be varied. We also examined two substrates containing a 5-methoxy group, a motif commonly found in bioactive oxindole-based compounds, with equally satisfying results (**3q**, **3r**). Furthermore, the remarkable reactivity of catalyst (*Ra*,*Ra*)-**1d** allows the reaction with less reactive aryl chlorides to proceed at room temperature with high yield and ee (**3f**).[10] Limitations became only apparent when the sterically highly congested substrate **2s** was tested. Here, a complete loss of enantioselectivity was accompanied with lower than normal reactivity. Nevertheless, the simple fact that catalyst *RaSa*-**1d** could promote such a difficult C–C coupling at room temperature is noteworthy. Substrate **2t** containing a heteroaromatic *N*-Me-3-indolyl moiety also undergoes smooth cyclization to give oxindole **3t** (94% yield, 86% ee). Contrary to what has been described,[11] the possible indolo-benzazepine byproduct arising from competitive Heck cyclization of the indolyl group was not observed. The framework of **3t** is of particular synthetic interest as it is widely found in natural products, and a range of total syntheses have been carried out based on this type of core structure.[12] We found that the selectivities of substrates which contain *meta*-substituted aromatic moieties could be further enhanced when (*Ra,Sa*)-**1d** was used as the precatalyst (**3c**, **3h**-**3j**).

To exemplify the generality of the present protocol and highlight catalyst **1d**'s excellent performance, substrate **2u** with two alkyl substituents at the α-position of the carbonyl moiety was also tested. The reaction with this more challenging substrate once again proceeded smoothly at ambient temperature to give oxindole **3u** with acceptable levels of enantioselectivity and excellent chemoselectivity (>20:1). To our knowledge, this is the first successful example of preparing enantiomerically enriched 3,3'-dialkyl oxindoles via a Pd-catalyzed α-arylation protocol.[13] Indeed, **3u** is a key intermediate for the synthesis (-)-physostigmine.[14]



Scheme 3. Scope of asymmetric synthesis of oxindoles with (*Ra,Ra*)-**1d**. [a] (*Ra,Sa*)-**1d** was used as the catalyst. [b] chloride used as the substrate.

Encouraged by these results, we became interested in ways of exclusively accessing the particularly useful diastereomer (*Ra,Ra*), as it would undoubtedly allow a more straightforward synthesis and use of these ligands. After testing several substitution patterns, we were pleased to find that placing a relatively rigid cyclooctyl group at the 2-position of the naphthyl moieties and ring closing the corresponding chiral diamine **A** at 120 °C for 2 hours (Scheme 4) generated virtually pure NHC salt (*Ra*,*Ra*)-**B**. The salt showed one set of signals and a diagnostic single peak for the C2 proton of the imidazolinium ring in the ^{1}H NMR spectrum.



Scheme 4. Synthesis of the Chiral NHC Complex

This salt was then used to synthesize the palladium cinnamyl complex (*Ra,Ra*)-**C** in high yield, the structure of which was unambiguously confirmed by single-crystal X-ray crystallography. Qualitative assessment of the structure shows both the relative bulk and the C_2-symmetry of the ligand. The overall steric demand of the ligand was then quantified via its buried volume $\%V_{Bur}$, a parameter describing the amount of volume in the first coordination sphere of a metal occupied by a given ligand and its topographic steric map.[15,16] To understand how the C_2-symmetry of the ligand affects the environment around the metal, we evaluated the $\%V_{Bur}$ in the four single quadrants of (*Ra,Ra*)-**C** and plotted the steric contour map highlighting zones of different steric pressures as shown in Figure 1.[16,17] This analysis was performed on the geometry of the (*Ra,Ra*)-**C** obtained from its crystal structure without further modifications. This analysis shows that the two quadrants where the 2-cyclooctyl groups are located are heavily hindered (bottom left and top right quadrants, $\%V_{Bur}$ ~46%), while the other two quadrants are clearly more open (bottom right and top left quadrants, $\%V_{Bur}$ ~35%). The map therefore demonstrates that the NHC ligand wraps around the metal center with almost perfect C_2-symmetry, a result that boded well for its application as an effective ancillary ligand in asymmetric transformations.

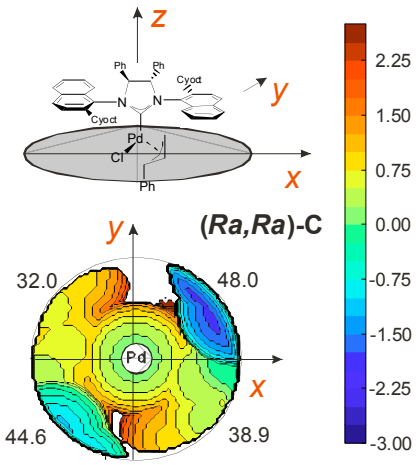
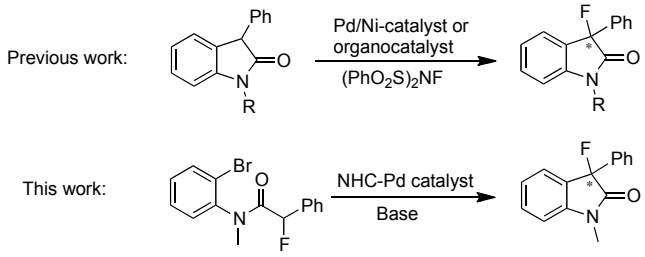


Figure 1. Steric contour maps of the NHC ligand in (*Ra,Ra*)-C. The complex is oriented as shown in the sketch. The number close to each quadrant is the $\%V_{ur}$ of this quadrant.

In earlier work, we had shown that relatives of (*Ra,Ra*)-**C** can be used as precatalysts in the α-arylation of amides to give enantioenriched oxindoles with quaternary carbon centers.[1] In this context, an attractive transformation involving such an α-arylation reaction would see the introduction of a fluorine atom onto the oxindole moiety, effectively resulting in the direct formation of enantioenriched 3-fluoro-3-aryl oxindoles. Owing to the often attractive properties of such fluorinated compounds for pharmaceutical applications,[18] incorporation of fluorine into organic molecules via enantioselective catalytic processes has been extensively investigated in the past decade. Up to now, such products are typically obtained via direct catalytic enantioselective fluorinations employing an electrophilic source of fluorine,[19] and no attempts at using enantioselective a-arylation reactions to gain access to these compounds have been documented (Scheme 5).[20]

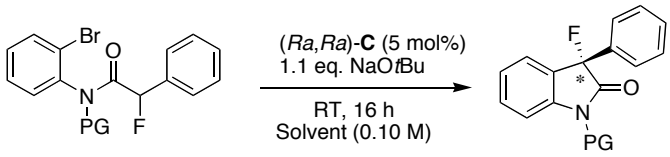


Scheme 5. Catalytic enantioselective synthesis of 3-fluoro-3-aryl oxindoles

We began our study by screening the protecting group at the *N*-substituent. The results in Table 2 reveal that when toluene was used as the solvent and NaO*t*Bu as the base, methyl protected starting product gave good yield (83%) and excellent

enantioselectivity (97% ee, entry 1). Using benzyl moiety retained the reactivity while decreasing the selectivity (entry 2). *Tert*-butoxycarbonyl (Boc) or 2-methoxyethoxymethyl (MEM) protected starting product did not show any reactivity (entries 3,4). The solvent study showed that toluene and benzene gave the best result in terms of yield and ee (entries 1, 6) while dioxane gave poor yield (entry 5) and *t*BuOH did not gave any product (entry 7). We also found out that it was crucial not to use excess of the base (NaO*t*Bu) to get high yield of the prodcut, as the substrate would otherwise decompose.

Table 2. Screening of protecting group and solvent

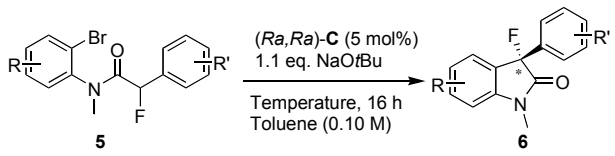


Entry	PG	Solvent	Yield(%)[a]	ee(%)[b]
1	Me	Toluene	83	97
2	Bn	Toluene	88	67
3	MEM	Toluene	0	----
4	Boc	Toluene	0	----
5	Me	Dioxane	35	88
6	Me	Benzene	82	95
7	Me	^{t}BuOH	0	-----

[a] Isolated yields; [b] Determined by chiral HPLC

Under optimized reaction conditions, different substrates were tested in the asymmetric α-arylation. As evidenced from data collected in Table 3, a variety of substrates are tolerated in this reaction. For instance, the introduction of electron-donating and electron-withdrawing groups (methoxy, methyl, phenyl, chloro, fluoro and trifluoromethyl) on the *ortho*-, *meta*-, or *para*-positions of the 3-phenyl

Table 3. Substrate Scope for the NHC-Pd Catalyzed α-Arylation.[a]



Entry	Substr.	R[b]	R'	T (°C)	Prod.	Yield (%)	ee (%)
1	**5a**	H	H	RT	**6a**	83	97
2	**5b**	5-Me	2-F	RT	**6b**	62	>99
3	**5c**	5-Me	4-Me	RT	**6c**	70	99
4	**5d**	5-MeO	1-Nap	50	**6d**	58	94
5	**5e**	5-MeO	H	RT	**6e**	82	99
6[c]	**5e**	5-MeO	H	RT	**6e**	89	91
7	**5f**	5-MeO	2-F	50	**6f**	82	99
8	**5g**	5-MeO	2-CF3	50	**6g**	85	98
9	**5h**	5-F	H	RT	**6h**	70	96
10	**5i**	5-F	2-F	RT	**6i**	76	>99
11	**5j**	6-CF3	H	RT	**6j**	81	94
12	**5k**	6-Me	2-Cl	60	**6k**	86	82
13	**5l**	H	2-Me	RT	**6l**	59	96
14	**5m**	H	2-F	RT	**6m**	65	>99
15[c]	**5m**	H	2-F	RT	**6m**	94	95
16	**5n**	H	3-MeO	RT	**6n**	50	95
17	**5o**	H	3-F	RT	**6o**	80	96
18	**5p**	H	4-Ph	RT	**6p**	61	94

[a] Conditions: **5** (0.20 mmol, 1.0 equiv), (*Ra,Ra*)-**C** (5.0 mol%), NaO*t*Bu (1.1 equiv), toluene (2.0 ml), RT or 50 °C, 16 h. We assume that all substrates follow the same reaction pathway to get the same relative configuration; [b] Numbering based on the oxindole product. [c] DME as solvent.

groups lead to excellent enantioselectivities and good yields within 16h at room temperature or 50 °C. Selected examples with substituents at the 5- and 6- position of the oxindole core lead to equally satisfying results. When DME is used as a solvent (entries 6, 15), reactivity increases while the selectivity is slightly lower. In several cases, virtually enantiopure products were obtained (**6b**, **6f**, **6i** and **6m**), a rather unique result when employing chiral, monodentate NHC ligands.[21]

The absolute stereochemistry of the products was deduced from an X-ray crystallographic analysis of compound **6o**, the stereogenic carbon center of which had the *S*-configuration.

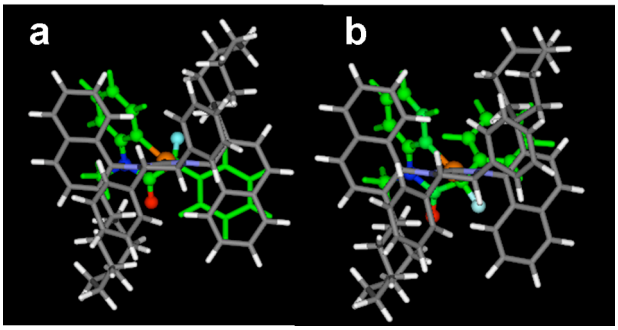


Figure 2. Optimized structure of the key intermediate before reductive elimination. The intermediates leading to the major *S* and minor *R* products are shown in parts a and b, respectively. C atoms of the NHC are colored in grey, C and H atoms of the substrate are colored in green.

To further support the assigned stereochemistry of the products and to gain first insights into the reaction mechanism, we performed a DFT study of the key intermediates in the case of the prototype substrate **5a**, corresponding to the expected compounds before final reductive elimination and release of product **6a**. The optimized geometries are reported in Figure 2. Structural analysis indicates that in the most stable intermediate of Figure 2a, leading to the experimentally favored *S* enantiomer, the aromatic ring that will form the skeleton of the oxindole product, and the Ph substituent on the final chiral C atom of the product are placed below the naphthyl ring, which is in the less buried quadrants highlighted by the steric map of Figure 1. By contrast, in the key intermediate of Figure 2b, leading to the experimentally less favored *R* enantiomer, the Ph substituent on the final chiral C atom of the product is placed below the cyclooctyl ring, which is in a buried quadrant highlighted by the steric contour map of Figure 1. According to calculations, the intermediate of Figure 2a is favored by 4.4 kcal/mol in toluene, a value correctly reflecting the high enantioselectivity observed.

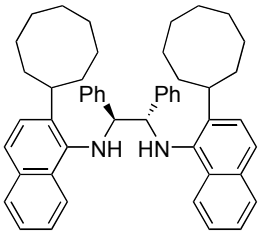
3.4 Conclusion

In conclusion, we have developed a new catalytic method for the enantioselective construction of carbon-fluorine bonds that relies on an asymmetric α-arylation protocol and have demonstrated its efficacy for the direct synthesis of 3-fluoro-3-aryl

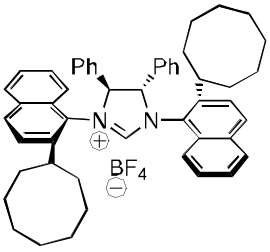
oxindoles. These target molecules were obtained in good yields and with excellent enantioselectivities when employing a new NHC ligand with a chiral N-heterocycle and naphthyl side chains that is easily accessed in virtually enantiopure form as a single diastereomer. Detailed mechanistic studies are in progress to shed light on the whole reaction pathway connecting reactants and products. Ongoing research aims to broaden the scope of this promising new way of enantioselective incorporation of fluorine into organic molecules and to test ligand (*Ra,Ra*)-**B** in other transformations.

3.5 Experimental Part

General: All reactions were carried out using standard Schlenk or glovebox (Mecaplex or Innovative Technology) techniques under nitrogen. KO*t*Bu was used after sublimation. 1-Bromo-2-cyclooctyl was prepared according to our previous report.[9e] α-Fluoro-α-arylcarboxylic acids were prepare according to reported procedure.[22] All other reagents were used as received unless otherwise noted. Solvents were purchased in the best quality available, degassed by purging thoroughly with nitrogen and dried over molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Solvents for NMR spectroscopy were degassed with nitrogen and dried over molecular sieves. NMR spectra were collected on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra were calibrated to the residual 1H and 13C of the solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). High-resolution electrospray ionization mass spectrometry was performed on a *FinniganMAT 900* (Finnigan MAT95, San Jose, CA; USA) double-focusing magnetic sector mass spectrometer (geometry BE). GC analysis was done on a ThermoQuest TraceGC2000. GC-MS analysis was done on a Finnigan Voyager GC8000 Top. X-ray crystallography was made on an *Agilent Technologies SuperNova* area-detector diffractometer using Mo *K*α radiation (λ = 0.71073 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler.



1*S*,2*S*-N,N'-Bis(2-cyclooctylnaphthalen-1-yl)-1,2-diphenylethane-1,2-diamine. A 250 mL schlenk flask was charged with $Pd(dba)_2$ (862 mg, 1.50 mmol), (±)-BINAP 1.12 g, 1.80 mmol), NaO*t*Bu (5.76 g, 60.0 mmol) and toluene (160 mL) and stirred for 5 min. 1-Bromo-2-cyclooctylnaphthalene (9.50 g, 30.0 mmol) and (1*S*,2*S*)-(-)-1,2-diphenylethylenediamine (3.10 g, 15.0 mmol) were then added and the solution was heated to 120 °C for 60 h. After cooling to room temperature, the resulting mixture was filtered through a celite and siliga filter and washed with CH_2Cl_2. The filtrate was concentrated and the residue was purified by flash chromatography (SiO_2, 1:3 CH_2Cl_2/n-hexane) to afford 1*S*,2*S*-N,N′- bis(2-cyclooctylnaphthalen-1-yl)-1,2-diphenylethane-1,2-diamine as a white solid (4.50 g, 44%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.64 (d, J = 8.3, 2H), 7.74 (d, J = 8.2, 2H), 7.50 (d, J = 8.6, 2H), 7.42-7.35 (m, 4H), 7.24 (d, J = 8.6 Hz, 2H), 6.96-6.90 (m, 10H), 5.10 (s, 2H), 4.87 (s, 2H), 3.08 (br, 2H), 1.84-0.97 (m, 28H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 140.94, 140.46, 138.20, 133.38, 130.14, 128.68, 128.49, 128.26, 127.28, 125.62, 125.37, 124.95, 124.69, 124.35, 68.80, 38.70, 35.39, 34.19, 27.32, 27.04, 27.01, 26.38, 26.15. HRMS (ESI): *m/z* : calcd for $C_{50}H_{57}N_2[M+1]^+$: 685.45163; found: 685.45156.



4*S*,5*S*-1,3-Bis(2-cyclooctylnaphthalen-1-yl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate ((*2*)-DiPhSICyoctNap·HBF$_4$). 1*S*,2*S*-N,N'-Bis(2-cyclooctylnaphthalen-1-yl)-1,2-diphenylethane-1,2-diamine (4.20 g, 6.13 mmol), ammonium tetrafluoroborate (1.29 g, 12.3 mmol), triethyl orthoformate (20 ml) and formic acid (0.2 ml) were heated to 120 °C and stirred for 2 h. The resulting suspension was filtered, and the residue was washed with ether (50 ml) to get a white powder (3.46 g, 72%). $[\alpha]^{25}_D$ = -198.8 (c = 0.65, CH_2Cl_2). ^{1}H NMR (DMSO-*d*6, 400 MHz): δ = 9.92 (s, 1H), 8.18-8.06 (m, 6H), 7.90 (t, J = 7.5 Hz, 2H), 7.75 (t, J = 7.5 Hz, 2H), 7.57 (d, J = 7.2 Hz, 4H), 7.46 (d, J = 8.7 Hz, 2H), 7.34-7.28 (m, 6H), 7.03 (s, 2H), 2.97 (br, 2H), 1.75-1.59 (m, 26H), 0.47 (br, 2H). ^{13}C {^{1}H} NMR (DMSO-*d*6, 125 MHz): 160.71, 147.96, 132.70, 131. 99, 130.89, 130.18, 129.82, 129.59, 129.49, 129.26, 129.20, 127.26, 125.59, 124.29, 122.32, 71.97, 41.04, 34.78, 32.46, 27.32, 26.53, 26.30,

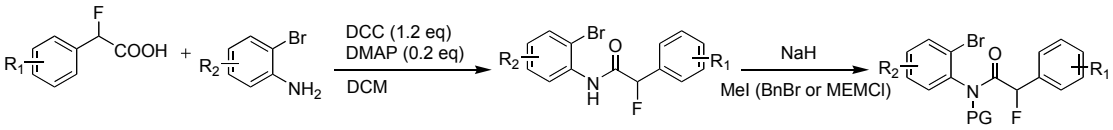
25.61, 25.18. ^{19}F NMR (DMSO-*d*6, 376 MHz): 148.33. HRMS (ESI): *m/z* : calcd for $C_{51}H_{55}N_2$ [M-BF_4]$^+$: 695.4360; found: 695.4356.

Chloro[(1,2,3-n)-3-phenyl-2-propenyl][*4S*,*5S*-*1*,3-Bis(2-cycoctyl-naphthalen-1-yl)-4,5-dihydro-4,5-diphenyl imidazol-2-ylidene] palladium(II) [((*2*)-DiPhSICyoctNap)Pd(cin)Cl]. (*2*)-DiPhSICyoctNap·HBF_4 (400 mg, 0.51 mmol), KO*t*Bu (57 mg, 0.51 mmol) and [Pd(cinnamyl)Cl]$_2$ (132 mg, 0.26 mmol) were mixed together in a round flask in the glovebox. Dry THF (45 mL) was added and the mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was separated by flash chromatography on siliga gel (n-hexane:ether 2:1→1:1) to afford the title product as a yellow solid (390 mg, 80%). Elemental analysis: calcd for $C_{60}H_{63}ClN_2Pd$: C, 75.54; H, 6.66; N, 2.94. Found: C, 75.29; H, 6.50; N, 2.90. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.44 (br, 2H), 7.83-7.71 (m, 6H), 7.52 (s, 2H), 7.26-6.98 (m, 17H), 6.04 (s, 2H), 4.97 (br, 0.6H), 4.43-4.17 (m, 1H), 3.24 (br, 1.9H), 2.47-2.11 (m, 2.5H), 1.67-1.27 (m, 25H), 0.34-0.13 (m, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 193.82, 192.47, 191.13, 180.58, 152.89, 147.78, 147.64, 142.58, 140.23, 137.72, 137.28, 134.51, 134.33, 134.17, 134.02, 133.04, 132.89, 132.79, 132.73, 132.70, 132.39, 131.33, 130.76, 130.29, 129.80, 129.29, 129.21, 129.15, 129.12, 129.03, 129.00, 128.93, 128.88, 128.85, 128.79, 128.75, 128.74, 128.66, 128.63, 128.60, 128.58, 128.54, 128.48, 128.22, 127.80, 127.28, 127.22, 126.34, 126.07, 125.82, 125.63, 125.44, 125.34, 125.23, 125.01, 124.52, 115.18, 75.40, 73.91, 72.92, 41.98, 41.64, 41.28, 34.80, 34.58, 32.36, 31.61, 28.86, 28.44, 28.14, 27.96, 27.55, 26.69, 26.36, 26.27, 25.63, 25.25, 23.64, 23.06. HRMS (ESI): *m/z* : calcd for $C_{60}H_{63}N_2Pd$ [M-Cl]$^+$: 917.4041; found: 917.4051.

***N*-(2-Bromophenyl)-*N*-(*tert*-butoxycarbonyl)-2-fluoro-2-phenylacetamide.** The mixture of amide (see bellow for synthesis of amide, 200 mg, 0.65 mmol), di-*tert*-butyl dicarbonate (176 mg, 0.81 mmol) and 4-dimethylaminopyridine (8.0 mg, 0.65 mmol) was stirred in 10 ml of CH_2Cl_2 for 20 h. Then the solved was removed under vacuum and the residue was purified by flash chromatography (Hexane/EtOAc) to afford the title as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62-7.53 (m, 3H), 7.43-7.26 (m, 4H), 7.21-7.17

(m, 1.5H), 7.11 (d, J = 10.6 Hz, 0.5H), 6.98 (d, J = 10.6 Hz, 0.5H), 6.86 (dd, J = 7.8, 1.6 Hz, 0.5H), 1.27 (s, 4.5H), 1.25 (s, 4.5H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 170.70, 170.44, 170.31, 170.05, 150.93, 150.88, 137.19, 136.71, 134.55, 134.04, 133.84, 133.10, 133.04, 130.32, 129.85, 129.81, 129.78, 129.66, 129.63, 129.39, 129.05, 129.00, 128.73, 128.71, 128.61, 128.57, 128.32, 128.30, 128.14, 123.21, 122.79, 91.35, 89.56, 84.27, 84.24, 27.53, 27.50. HRMS (ESI): *m/z* : calcd for $C_{19}H_{19}BrFNNaO_3$ $[M+Na]^+$: 430.04246; found: 430.04268.

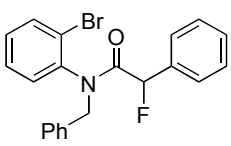
Synthesis of the benzyl, 2-methoxyethoxymethyl and methyl protected substrates



α-Fluoro-α-arylcarboxylic acid (2.0 mmol) , aniline (2.0 mmol) and DMAP (4-dimethylaminopyridine, 0.40 mmol) were dissolved in 10 ml of CH_2Cl_2. Upon cooling to 0 °C, DCC (*N,N'*-Dicyclohexylcarbodiimide, 2.4 mmol) in 10 ml CH_2Cl_2 was added in 5 min. The mixture was gradually warmed to RT and then leave overnight. The suspension was filtered and the filtrate was dried and then purified by flash chromatography (EtOAc/Hexane) to get the unprotected amide.

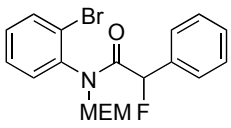
To a solution of the corresponding amide (1.0 mmol, 1.0 eq) in 10 ml of THF, 1.1 eq. NaH (60% in mineral oil) was added in small portions at 0 °C, and the resulting mixture was stirred for 30 min. Subsequently, 1.1 eq. MeI (or BnBr, or MEMCl) in THF was added dropwise at 0 °C, and the resulting mixture was stirred overnight at RT. The reaction mixture was then filtered through a pad of silica/celite, washed with CH_2Cl_2, and dried in *vacuo*. The residue was then purified by flash chromatography (EtOAc/Hexane) to afford the corresponding substrate.

***N*-(2-Bromophenyl)-*N*-benzyl-2-fluoro-2-phenylacetamide.** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (d, J = 8.0 Hz, 0.6H), 7.53-7.51 (m, 0.4H), 7.32-7.05 (m, 11.4H), 6.87 (t, J = 7.7 Hz, 0.6H), 6.80-6.77 (m, 0.4H), 6.04 (d, J = 7.8 Hz, 0.6H), 5.74-5.35 (m, 2H), 4.12 (d, J = 14.3 Hz, 0.6H), 3.94 (d, J = 14.2 Hz, 0.4H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 168.42, 168.16, 167.94, 167.68, 138.84, 138.81, 136.64, 136.56, 134.77, 134.57,

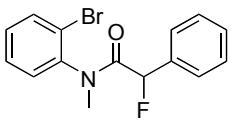


134.50, 134.22, 134.11, 133.91, 132.60, 130.82, 130.77, 130.29, 130.26, 130.13, 130.10, 130.06, 129.79, 129.09, 129.08, 128.95, 128.91, 128.68, 128.64, 128.40, 128.36, 128.32, 128.22, 125.20, 124.50, 90.78, 90.32, 88.99, 88.54, 52.70, 52.19. HRMS (ESI): *m/z* : calcd for $C_{21}H_{17}BrFNNaO$ $[M+Na]^+$: 420.03698; found: 420.03663.

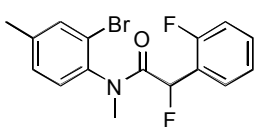
***N*-(2-Bromophenyl)-*N*-methoxyethoxymethyl-2-fluoro-2-phenylacetamide.** ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (dd, *J* = 8.1, 1.2Hz, 0.6H), 7.46-6.98 (m, 7.8H), 6.56 (dd, *J* = 7.8, 1.4 Hz, 0.6H), 5.74-5.36 (m, 2H), 4.59 (d, *J* = 10.7 Hz, 0.6H), 4.49 (d, *J* = 10.7 Hz, 0.4H), 3.88-3.66 (m, 2H), 3.52-3.38 (m, 2H), 3.31 (s, 1.2 H), 3.24 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 169.25, 169.04, 168.83, 168.63, 137.74, 137.62, 133.95, 133.92, 133.79, 133.65, 133.11, 133.02, 132.95, 132.40, 130.78, 130.67, 130.11, 130.09, 129.93, 129.90, 128.80, 128.79, 128.76, 128.63, 128.62, 128.53, 128.27, 128.24, 128.12, 128.08, 124.62, 123.74, 90.22, 89.61, 88.78, 88.18, 77.85, 77.84, 77.56, 71.75, 71.63, 69.08, 68.84, 59.12, 59.01. HRMS (ESI): *m/z* : calcd for $C_{18}H_{19}BrFNNaO_3$ $[M+Na]^+$: 418.04246; found: 418.04269.



***N*-(2-Bromophenyl)-*N*-methyl-2-fluoro-2-phenylacetamide (5a).** ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.69 (dd, *J* = 8.0, 1.3 Hz, 0.6H), 7.52 (dd, *J* = 8.1, 1.3 Hz, 0.4H), 7.42-7.04 (m, 7.4H), 6.59 (dd, J = 7.8, 1.6 Hz, 0.6H), 5.66 (d, *J* = 47.2 Hz, 0.4H), 5.41 (d, *J* = 47.2 Hz, 0.6H), 3.22 (s, 1.2H), 3.20 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 100MHz): 167.66, 140.36, 134.17, 134.09, 133.84, 133.55, 131.29, 130.31, 130.18, 129.75, 129.72, 129.54, 129.51, 128.84, 128.60, 128.59, 128.57, 128.44, 128.43, 128.11, 128.06, 127.75, 127.69, 124.34, 123.47, 90.12, 89.69, 88.33, 87.90, 36.51, 36.50, 36.49. HRMS (ESI): *m/z* : calcd for $C_{15}H_{13}BrFNNaO$ $[M+Na]^+$: 344.00568; found: 344.00577.



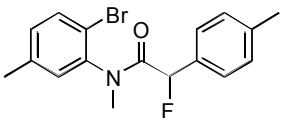
***N*-(2-Bromo-4-methylphenyl)-*N*-methyl-2-fluoro-2-(2-fluorophenyl)acetamide**



(5b). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.55-7.50 (m, 1.6H), 7.34-7.28 (m, 1.8 H), 7.26-7.23 (m, 0.4H), 7.16-7.10 (m, 1H), 6.92-6.86 (m, 1.6H), 6.46 (d, *J* = 8.0 Hz, 0.6H), 6.03 (d, *J* =

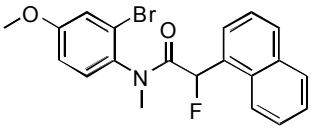
47.1 Hz, 0.4H), 6.03 (d, *J* = 47.1 Hz, 0.6H), 3.22 (s, 1.2H), 3.20 (s, 1.8H), 2.38 (s, 1.2 H), 2.36 (s, 1.8H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 167.55, 167.34, 161.22, 159.23, 141.05, 141.04, 127.34, 137.03, 134.31, 131.80, 131.77, 131.73, 131.70, 131.60, 131.57, 131.53, 131.51, 130.05, 129.99, 129.97, 129.96, 129.94, 129.79, 129.59, 129.46, 129.44, 129.42, 124.61, 124.59, 124.58, 124.56, 124.46, 124.45, 124.44, 124.42, 123.22, 122.80, 122.10, 121.99, 121.93, 121.82, 115.44, 115.43, 115.32, 115.31, 115.27, 115.26, 115.15, 115.14, 82.66, 82.62, 82.31, 82.27, 81.24, 81.21, 80.90, 80.86, 36.56, 36.55, 36.54, 36.53, 20.84, 20.83. HRMS (ESI): *m/z* : calcd for $C_{16}H_{14}BrF_2NNaO$ $[M+Na]^+$: 376.0119; found: 376.0115.

***N*-(2-Bromo-5-methylphenyl)-*N*-methyl-2-fluoro-2-(4-methylphenyl)acetamide**



(5c). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49 (s, 0.6H), 7.33 (s, 0.4H), 7.19-7.18(m, 0.8H), 7.05-7.03(m, 2H), 6.99-6.95 (m, 2H), 6.90-6.88 (m, 0.6H), 6.46 (d, *J* = 7.9 Hz, 0.6H), 5.60 (d, *J* = 47.6 Hz, 0.4H), 5.36 (d, *J* = 48.1 Hz, 0.6H), 3.17 (s, 1.2H), 3.15 (s, 1.8H), 2.35 (s, 1.2H), 2.33 (s, 1.8H), 2.30-2.29 (m, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125MHz): 168.29, 168.08, 167.96, 167.75, 140.93, 140.88, 139.81, 139.78, 139.50, 139.47, 138.03, 137.63, 134.35, 134.12, 131.45, 131.29, 130.83, 130.78, 130.66, 129.63, 129.59, 129.30, 129.25, 129.24, 129.09, 129.08, 128.17, 128.14, 127.85, 127.81, 123.82, 122.93, 89.59, 89.19, 88.17, 87.77, 36.48, 21.34, 20.90, 20.88. HRMS (ESI): *m/z* : calcd for $C_{17}H_{17}BrFNNaO$ $[M+Na]^+$: 372.03698; found: 372.03651.

***N*-(2-Bromo-4-methoxyphenyl)-*N*-methyl-2-fluoro-2-(1-naphthyl)acetamide**



(5d). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.86-7.67 (m, 3H), 7.42-6.68 (m, 6H), 6.33 (d, *J* = 47.0 Hz, 0.4H), 6.15 (d, *J* = 47.0 Hz, 0.6H), 6.07 (d, *J* =8.8 Hz, 0.5H), 6.97 (d, *J* = 8.8 Hz, 0.5H), 3.77 (s, 0.3H), 3.72 (s, 0.9H), 3.63 (s, 1.8H), 3.18 (s, 1.2H), 3.16 (s, 1.8H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 171.44, 168,96, 168.75, 168.52, 168.32, 160.23, 159.98, 133.94, 133.80, 133.32, 132.79, 131.64, 131.44, 131.23, 130.70, 130.63, 130.60, 130.55, 130.43, 129.31, 128.77, 128.73, 128.14, 128.09, 127.83, 127.78, 127.75, 127.02, 126.73, 126.22, 126.17, 125.94, 125.71, 124.32, 123.69, 123.60, 123.28, 118.96, 118.91, 118.80, 114.96, 114.82, 114.08, 88.73, 88.64, 87.30, 87.22,

56.05, 55.95, 37.14. HRMS (ESI): *m/z* : calcd for $C_{20}H_{17}BrFNNaO_2$ $[M+Na]^+$: 424.03189; found: 424.03189.

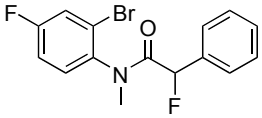
***N*-(2-Bromo-4-methoxyphenyl)-*N*-methyl-2-fluoro-2-phenylacetamide (5e).** ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.22-7.18 (m, 4H), 7.10-7.06 (m, 2H), 7.01 (d, *J* = 2.8 Hz, 0.4H), 6.90 (dd, *J* = 8.7, 2.8 Hz, 0.4H), 6.58 (dd, *J* = 8.8, 2.8 Hz, 0.6H), 6.44 (d, *J* = 8.7 Hz, 0.6H), 5.64 (d, *J* = 47.7 Hz, 0.4H), 5.42 (d, *J* = 47.7 Hz, 0.6H), 3.80 (s, 1.2H), 3.78 (s, 1.8H), 3.17 (s, 1.2H), 3.14 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 100 MHz): 168.56, 168.30, 168.21, 167.95, 160.38, 160.31, 134.69, 134.49, 134.07, 133.87, 133.49, 133.10, 131.79, 130.66, 129.95, 129.92, 129.73, 129.71, 128.80, 128.78, 128.64, 128.63, 128.35, 128.31, 128.04, 127.99, 125.04, 119.15, 118.70, 114.64, 114.61, 90.28, 89.81, 88.50, 88.04, 56.10, 56.07, 36.88, 36.87. HRMS (ESI): *m/z* : calcd for $C_{16}H_{15}BrFNNaO_2$ $[M+Na]^+$: 374.01624; found: 374.01642.

***N*-(2-Bromo-4-methoxyphenyl)-*N*-methyl-2-fluoro-2-(2-fluorophenyl)acetamide (5f).** ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.52-7.48 (m, 1H), 7.31-7.08 (m, 3H), 7.01 (d, *J* = 2.8 Hz, 0.4H), 6.92-6.84 (m, 1.4H), 6.56 (dd, *J* = 8.8, 2.8 Hz, 0.6H), 6.41 (d, *J* = 8.8 Hz, 0.6H), 6.00 (d, *J* = 47.1 Hz, 0.4H), 5.80 (d, *J* = 47.1 Hz, 0.6H), 3.79 (s, 1.2H), 3.77 (s, 1.8H), 3.18 (s, 1.2H), 3.16 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 100 MHz): 160.48, 160.39, 133.03, 132.70, 131.95, 131.92, 131.87, 131.84, 131.79, 131.76, 131.71, 131.68, 131.13, 130.69, 130.28, 130.25, 129.73, 129.70, 124.87, 124.84, 124.83, 124.81, 124.74, 124.72, 124.50, 124.08, 119.24, 118.72, 115.71, 115.69, 115.58, 115.50, 115.48, 115.37, 114.87, 114.83, 83.09, 83.05, 82.72, 82.68, 81.32, 81.27, 80.96, 80.92, 56.11, 36.96, 36.95. HRMS (ESI): *m/z* : calcd for $C_{16}H_{14}BrF_2NNaO_2$ $[M+Na]^+$: 392.00734; found: 392.00746.

***N*-(2-Bromo-4-methoxyphenyl)-*N*-methyl-2-fluoro-2-(2-trifluoromethylphenyl) acetamide (5g).** ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.90-6.94 (m, 6H), 6.57-6.54 (m, 0.5H), 6.39 (d, *J* = 8.8 Hz, 0.5H), 6.10 (d, *J* = 47.4 Hz, 0.4H), 5.90 (d, *J* = 47.4 Hz, 0.6H), 3.82 (s, 1.2H), 3.79 (s, 1.8H), 3.27 (s, 1.2H), 3.25 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125

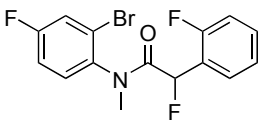
MHz): 170.31, 167.61, 167.41, 167.29, 167.09, 160.29, 160.23, 159.88, 134.94, 132.73, 132.71, 132.56, 132.55, 132.41, 132.40, 132.35, 132.34, 131.69, 131.68, 130.92, 130.87, 130.72, 130.26, 130.02, 129.99, 129.96, 129.92, 129.87, 129.84, 126.91, 126.20, 126.18, 126.15, 126.14, 125.93, 125.92, 125.89, 125.88, 125.84, 124.13, 123.80, 123.29, 118.94, , 118.76, 118.60, 114.88, 114.71, 114.56, 85.40, 85.38, 84.68, 83.97, 83.96, 55.87, 57.14, 36.93,36.27. HRMS (ESI): *m/z* : calcd for $C_{17}H_{14}BrF_4NNaO_2$ $[M+Na]^+$: 442.00417; found: 442.00426

***N*-(2-Bromo-4-fluorophenyl)-*N*-methyl-2-fluoro-2-phenylacetamide (5h).** ^1H



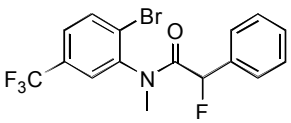
NMR ($CDCl_3$, 400 MHz): δ = 7.47-7.09 (m, 6.8H), 6.83 (td, *J* = 7.7, 2.8 Hz, 0.6H), 6.58-6.56 (m, 0.6H), 5.68 (d, *J* = 47,6 Hz, 0.4H), 5.43 (d, *J* = 47,6 Hz, 0.6H), 3.22 (s, 1.2H), 3.21 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 168.14, 167.93, 167.84, 167.64, 163.14, 163.05, 161.12, 161.03, 137.16, 137.13, 136.80, 136.77, 134.31, 134.15, 133.72, 133.55, 132.57, 132.49, 131.39, 131.32, 130.14, 130.11, 129.89, 129.86, 128.94, 128.92, 128.77, 128.76, 128.26, 128.22, 127.86, 127.82, 125.32, 125.24, 124.32, 124.24, 121.49, 121.29, 121.26, 121.06, 116.24, 116.07, 116.05, 115.87, 90.24, 89.88, 88.81, 88.44, 36.83. HRMS (ESI): *m/z* : calcd for $C_{15}H_{12}BrF_2NNaO$ $[M+Na]^+$: 361.9968; found: 361.9965.

***N*-(2-Bromo-4-fluorophenyl)-*N*-methyl-2-fluoro-2-(2-fluorophenyl)acetamide**



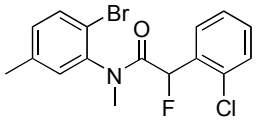
(5i). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.56-7.12 (m, 5H), 6.96-6.79 (m, 1.6 H), 6.59-6.54 (m, 0.4H), 6.02 (d, *J* = 47.0 Hz, 0.4H), 5.80 (d, *J* = 47.0 Hz, 0.6H), 3.23 (s, 1.2H), 3.19 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 167.50, 167.15, 166.80, 163.70, 163.61, 161.91, 161.85, 161.79, 160.33, 160.24, 158.60, 158.53, 158.47, 136.48, 136.43, 136.20, 136.15, 131.96, 131.92, 131.85, 131.81, 131.75, 131.71, 131.64, 131.59, 131.28, 131.16, 129.95, 129.90, 129.86, 129.40, 129.36, 129.32, 124.79, 124.76, 124.71, 124.65, 124.60, 124.57, 124.42, 124.15, 124.02, 121.34, 121.26, 121.01, 120.92, 116.38, 116.09, 116.00, 115.70, 115.56, 115.54, 115.43, 115.28, 115.26, 115.14, 83.11, 83.05, 82.82, 82.76, 80.73, 80.67, 80.46, 80.40, 36.63. HRMS (ESI): *m/z* : calcd for $C_{15}H_{11}BrF_3NNaO$ $[M+Na]^+$: 379.98683; found: 379.98682.

***N*-(2-Bromo-5-trifluoromethyl-phenyl)-*N*-methyl-2-fluoro-2-phenylacetamide**



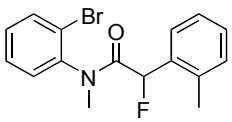
(5j). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78 (d, J = 8.4 Hz, 0.6H), 7.63 (d, J = 8.3 Hz, 0.4H), 7.45-7.18 (m, 3.4H), 7.02-6.95 (m, 2H), 6.70 (s, 0.6H), 5.64 (d, J = 47.8 Hz, 0.4H), 5.30 (d, J = 47.8 Hz, 0.6H), 3.18 (s, 1.2H), 3.16 (s, 1.8H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 167.82, 167.59, 167.56, 167.35, 141.71, 141.19, 134.93, 134.80, 134.03, 133.90, 133.93, 133.69, 131.70, 131.36, 130.38, 130.35, 129.11, 129.09, 128.92, 128.89, 128.84, 128.12, 128.10, 128.09, 128.01, 127.43, 127.40, 127.22, 127.18, 127.14, 127.13, 127.11, 127.02, 126.99, 126.95, 124.58, 124.24, 121.88, 121.53, 118.83, 90.93, 90.72, 89.10, 88.92, 36.92, 36.67. HRMS (ESI): *m/z* : calcd for $C_{16}H_{12}BrF_4NNaO$ $[M+Na]^+$: 411.99306; found: 411.99346.

***N*-(2-Bromo-5-methylphenyl)-*N*-methyl-2-fluoro-2-(2-chlorophenyl)acetamide**



(5k). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59-7.52 (m, 1H), 7.43 (d, J = 8.2 Hz, 0.67H), 7.30-7.11 (m, 3.67H), 6.96-6.90 (m, 1H), 6.12 (d, J = 47.3 Hz, 0.33H), 6.10 (s, 0.67H), 5.84 (d, J = 47.3 Hz, 0.67H), 3.15 (s, 1H), 3.12 (s, 2H), 2.27 (s, 1H), 1.93 (s, 2H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 168.02, 167.76, 167.62, 167.36, 140.28, 140.10, 139.79, 139.65, 135.41, 135.37, 134.43, 134.38, 134.35, 134.02, 132.93, 132.73, 132.01, 131.93, 131.81, 131.75, 131.69, 131.53, 131.50, 131.34, 131.31, 131.22, 130.76, 130.71, 130.39, 130.35, 129.79, 129.77, 129.73, 129.71, 127.91, 127.88, 127.74, 127.72, 120.40, 120.20, 86.79, 86.01, 85.01, 84.25, 37.04, 36.88, 36.87, 21.29, 21.07. HRMS (ESI): *m/z* : calcd for $C_{16}H_{14}BrClFNNaO$ $[M+Na]^+$: 391.98235; found: 391.98270.

***N*-(2-Bromophenyl)-*N*-methyl-2-fluoro-2-(2-methylphenyl)acetamide (5l).** ^{1}H



NMR ($CDCl_3$, 400 MHz): δ = 7.64 (d, J = 8.1 Hz, 0.6H), 7.46-6.94 (m, 6.8H), 6.34 (d, J = 8.2 Hz, 0.6H), 5.91 (d, J = 47.6 Hz, 0.4H), 5.65 (d, J = 47.6 Hz, 0.6H), 3.22 (s, 1.2H), 3.19 (s, 1.8H), 1.84 (s, 1.2H), 1.70 (s, 1.8H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125MHz): 170.71, 168.36, 168.16, 167.96, 167.76, 142.53, 140.57, 140.02, 137.66, 137.63, 137.35, 137.32, 136.82, 134.25, 133.95, 133.74, 133.71, 132.47, 132.33, 131.44, 131.29, 131.26, 130.61, 130.59, 130.55, 130.53, 130.24, 130.22, 130.09, 129.98, 129.95, 129.91, 129.84, 129.65, 129.63, 129.19, 129.15, 129.03, 129.01, 128.67, 128.51, 128.50,

128.49, 126.89, 126.48, 126.45, 126.22, 126.20, 125.85, 124.19, 123.56, 123.45, 87.27, 85.85, 39.08, 36.61, 36.48, 36.12, 19.66, 18.37, 18.08. HRMS (ESI): *m/z* : calcd for $C_{16}H_{15}BrFNNaO$ $[M+Na]^+$: 358.02133; found: 358.02162.

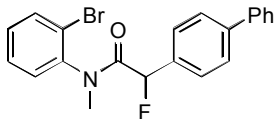
***N*-(2-Bromo-phenyl)-*N*-methyl-2-fluoro-2-(2-fluorophenyl) acetamide (5m).** ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.67-7.07 (m, 6.4 H), 6.86 (br, 1H), 6.55 (s, 0.6H), 6.01 (d, *J* = 47.1 Hz, 0.4H), 5.78 (d, *J* = 47.1 Hz, 0.6H), 3.23 (s, 1.2H), 3.21 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 167.41, 167.20, 167.05, 166.85, 161.33, 161.27, 161.23, 159.34, 159.30, 159.27, 159.24, 140.07, 139.80, 134.09, 133.94, 131.83, 131.81, 131.76, 131.74, 131.68, 131.65, 131.61, 131.59, 130.61, 130.47, 130.45, 130.15, 130.01, 129.50, 129.47, 129.45, 129.12, 128.73, 124.66, 124.54, 123.76, 123.38, 122.04, 121.93, 121.87, 121.76, 121.12, 121.02, 120.95, 120.85, 115.46, 115.35, 115.29, 115.17, 82.69, 82.66, 82.33, 82.30, 81.28, 81.24, 80.92, 80.89, 36.55, 36.53 HRMS (ESI): *m/z* : calcd for $C_{15}H_{12}BrF_2NNaO$ $[M+Na]^+$: 361.99625; found: 361.99622.

***N*-(2-Bromophenyl)-*N*-methyl-2-fluoro-2-(3-methoxyphenyl)acetamide (5n).** ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.74-7.15 (m, 4.4H), 6.90-6.88 (m, 1H), 6.71-6.61 (m, 2.6H), 5.68 (d, *J* = 47.6 Hz, 0.4H), 5.42 (d, *J* = 47.6 Hz, 0.6H), 3.76 (s, 3H), 3.25 (s, 1.2H), 3.23 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 100 MHz): 168.02, 167.76, 167.49, 159.92, 159.90, 159.79, 140.87, 140.53, 135.88, 135.68, 135.26, 135.05, 134.27, 134.03, 131.57, 130.56, 130.55, 130.37, 129.79, 129.78, 129.67, 129.08, 128.85, 124.54, 123.63, 120.60, 120.56, 120.28, 120.22, 116.16, 116.14, 116.13, 116.01, 115.98, 113.05, 113.00, 112.72, 112.67, 90.23, 89.80, 88.44, 88.01, 55.49, 55.48, 36.72, 36.70. HRMS (ESI): *m/z* : calcd for $C_{16}H_{15}BrFNNaO_2$ $[M+Na]^+$: 374.01679; found: 374.01668.

***N*-(2-Bromophenyl)-*N*-methyl-2-fluoro-2-(3-fluorophenyl)acetamide (5o).** ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.74-7.18 (m, 4.5H), 7.06-7.01 (m, 1H), 6.86-6.82 (m, 1H), 6.72 (d, *J* = 8.8 Hz, 0.5 H), 5.67 (d, *J* = 47.4 Hz, 0.5H), 5.45 (d, *J* = 47.4 Hz, 0.5H), 3.24 (s, 1.5H), 3.23 (s, 1.5H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 167.35, 167.14, 167.02, 166.82, 163.54,

163.51, 161.55, 140.40, 140.11, 136.56, 136.50, 136.39, 136.34, 134.14, 133.97, 131.11, 130.59, 130.58, 130.27, 130.26, 130.20, 130.19, 130.15, 130.11, 130.05, 129.02, 128.76, 124.13, 123.63, 123.60, 123.59, 123.57, 123.40, 123.36, 123.34, 123.32, 123.29, 116.85, 116.83, 116.68, 116.66, 116.61, 116.59, 116.44, 116.42, 114.98, 114.94, 114.80, 114.77, 114.72, 119.59, 114.54, 89.08, 89.07, 88.66, 88.64, 87.65, 87.63, 87.22, 87.20, 36.60, 36.59, 36.54. HRMS (ESI): *m/z* : calcd for $C_{15}H_{12}BrF_2NNaO$ $[M+Na]^+$: 361.99625; found: 361.99611.

***N*-(2-Bromo-phenyl)-*N*-methyl-2-fluoro-2-(4-biphenyl) acetamide (5p).** ^1H NMR

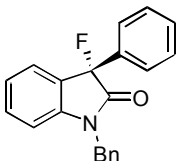


($CDCl_3$, 400 MHz): δ = 7.38-7.18 (m, 10H), 7.12-7.07 (m, 2.4H), 6.64 (d, J = 7.8 Hz, 0.6H), 5.66 (d, J = 47.5 Hz, 0.4H), 5.43 (d, J = 47.5 Hz, 0.6H), 3.20 (s, 1.2H), 3.19 (s, 1.8H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 168.16, 167.90, 167.86, 167.61, 142.87, 142.84, 142.69, 142.66, 140.98, 140.79, 140.64, 140.47, 140.46, 134.38, 134.14, 133.51, 133.31, 132.93, 132.72, 131.56, 130.62, 130.45, 129.15, 129.06, 128.91, 128.78, 128.74, 128.45, 128.39, 128.02, 127.85, 127.52, 127.50, 127.42, 127.36, 124.58, 123.73, 90.07, 89.71, 88.28, 87.92, 36.77, 36.76. HRMS (ESI): *m/z* : calcd for $C_{21}H_{17}BrFNNaO$ $[M+Na]^+$: 420.03698; found: 420.03657.

Catalyzed α-arylation

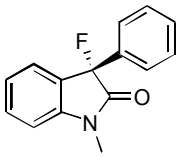
General catalysis procedure: In the glovebox, a vial (10 mL screw-cap threaded) equipped with a stir-bar was charged with palladium catalyst (9.5 mg, 5.0 mol%), sodium *tert*-butoxide (21.1 mg, 0.22 mmol), then the substrate **(**0.20 mmol) and toluene (2 ml) were added. The mixture was stirred at room temperature for 16 h before flitering throuth celite. Alternatively, if heating was needed, the vial was sealed a Teflon®-lined screw cap and the mixture was stirred at 50 °C for 16 h before filtering through celite. The solvent was removed in vacuo and the residue was purified by flash chromatography. The product was analyzed by chiral HPLC analysis.

(*S*)- 1-Benzyl-3-fluoro-3-phenylindolin-2-one. Room temperature, white solid, 88% yield. $[\alpha]^{25}_D$ = 77.8 (c = 0.69, $CHCl_3$), 67% ee [Chiralcel OJ-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 36.0 min (minor) and 62.6 min (major)]. ^1H NMR

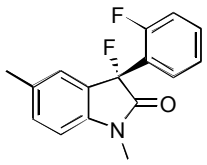


($CDCl_3$, 400 MHz): δ = 7.41-7.26 (m, 12H), 7.08 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 4.96 (d, J = 15.7 Hz, 1H), 4.83 (d, J = 15.7 Hz, 1H). ^{13}C {^1H} NMR ($CDCl_3$, 100 MHz): 172.96, 172.72, 144.09, 144.04, 136.43, 136.16, 135.40, 131.72, 131.68, 129.55, 129.53, 129.21, 128.93, 128.16, 127.54, 127.53, 127.35, 127.17, 126.53, 126.52, 126.20, 126.13, 123.87, 123.85, 110.22, 110.20, 44.31. ^{19}F NMR ($CDCl_3$, 376 MHz): -152.90. HRMS (ESI): *m/z* : calcd for $C_{21}H_{16}FNNaO$ $[M+Na]^+$: 340.11081; found: 340.11049.

(*S*)-3-Fluoro-1-methyl-3-phenylindolin-2-one (6a). Room temperature, colorless oil, 83% yield. $[\alpha]^{25}_D$ = 110.7 (c = 1.9, CH_2Cl_2), 97% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 7.47 min (minor) and 9.11 min (major)]. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45-7.31 (m, 7H), 7.13 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 3.21 (s, 3H). ^{13}C {^1H} NMR ($CDCl_3$, 125 MHz): 172.56, 172.36, 144.69, 144.65, 135.99, 135.77, 131.57, 131.54, 129.26, 128.58, 126.92, 126.78, 126.20, 126.00, 125.95, 123.58, 108.85, 93.97, 92.47, 26.52. ^{19}F NMR ($CDCl_3$, 376 MHz): -152.90. HRMS (ESI): *m/z* : calcd for $C_{15}H_{12}FNNaO$ $[M+Na]^+$: 264.07951; found: 264.07945.

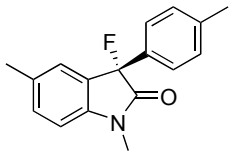


(*R*)-3-Fluoro-1,5-dimethyl-3-(2-fluorophenyl)-indolin-2-one (6b). Room temperature, colorless oil, 62% yield. $[\alpha]^{25}_D$ = -45.3 (c = 0.38, CH_2Cl_2), 99.5% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 6.44 min (minor) and 7.81 min (major)].



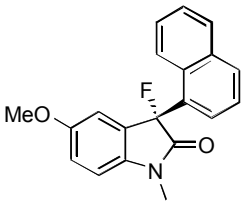
^1H NMR ($CDCl_3$, 400 MHz): δ = 7.75 (t, J = 7.7 Hz, 1H), 7.33-7.13 (m, 3H), 6.94-6.89 (m, 2H), 6.74 (d, J = 7.0 Hz, 1H), 3.22 (s, 3H), 2.21 (s, 3H). ^{13}C {^1H} NMR ($CDCl_3$, 125 MHz): 171.46, 171.29, 159.50, 159.46, 157.53, 157.49, 142.17, 142.13, 133.13, 133.10, 131.87, 131.84, 130.61, 130.55, 127.02, 127.00, 126.93, 126.91, 126.47, 126.32, 126.00, 124.66, 124.56, 124.42, 124.41, 124.39, 124.38, 115.90, 115.89, 115.74, 115.72, 108.60, 108.58, 92.06, 90.57, 26.59, 20.96. ^{19}F NMR ($CDCl_3$, 376 MHz): -114.44, -159.26. HRMS (ESI): *m/z* : calcd for $C_{16}H_{13}F_2NNaO$ $[M+Na]^+$: 296.08574; found: 296.08557.

(*S*)-3-Fluoro-1,5-dimethyl-3-(4-methylphenyl)-indolin-2-one (6c). Room



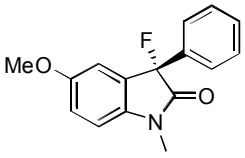
temperature, white solid, 70% yield. $[\alpha]^{27}_{D}$ = 131.2 (c = 0.45, CH_2Cl_2), 99% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 12.83 min (minor) and 13.76 min (major)]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.18 (d, *J* = 8.1 Hz, 2H), 7.13-7.04 (m, 4H), 6.69 (d, *J* = 8.0 Hz, 1H), 3.08 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 172.69, 172.49, 142.24, 142.19, 139.18, 139.17, 133.24, 133.22, 133.20, 132.98, 131.67, 131.64, 130.70, 129.25, 129.21, 127.44, 127.03, 126.89, 126.81, 125.95, 125.90, 108.58, 108.57, 94.17, 92.68, 26.51, 21.26, 21.05. ^{19}F NMR ($CDCl_3$, 376 MHz): -152.29. HRMS (ESI): *m/z* : calcd for $C_{17}H_{16}FNNaO$ $[M+Na]^+$: 292.11081; found: 292.11092.

(*S*)-3-Fluoro-5-methoxy-1-methyl-3-(1-naphthyl)-indolin-2-one (6d). 50 °C**,**



white solid, 58% yield. $[\alpha]^{25}_{D}$ = 56.5 (c = 0.92, CH_2Cl_2), 94% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 12.75 min (minor) and 17.92 min (major)].)]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88-7.70 (m, 4H), 7.48-7.38 (m, 3H), 6.97-6.84 (m, 3H), 3.68 (s, 3H), 3.31 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 172.15, 171.97, 156.62, 156.59, 137.61, 137.57, 134.27, 130.40, 129.01, 128.77, 128.62, 126.65, 125.86, 124.86, 116.25, 116.22, 112.82, 109.66, 109.65, 55.80, 26.75. ^{19}F NMR ($CDCl_3$, 376 MHz): -147.83. HRMS (ESI): *m/z* : calcd for $C_{20}H_{16}FNNaO_2$ $[M+Na]^+$: 344.10573; found: 344.10538.

(*S*)-3-Fluoro-5-methoxy-1-methyl-3-phenyl-indolin-2-one (6e). Room



temperature**,** white solid, 82% yield. $[\alpha]^{27}_{D}$ = 181.6 (c = 1.40, CH_2Cl_2), 99% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 9.05 min (minor) and 11.62 min (major)]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (br, 5H), 6.96-6.92 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 3.76 (s, 3H), 3.18 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 156.90, 156.87, 138.23, 138.18, 136.37, 129.50, 129.48, 128.85, 128.14, 126.21, 126.15, 116.53, 116.51, 113.19, 109.68, 109.66, 94.76, 92.89, 56.18, 26.85. ^{19}F NMR ($CDCl_3$, 376 MHz): -153.48. HRMS (ESI): *m/z* : calcd for $C_{16}H_{14}FNNaO_2$ $[M+Na]^+$: 294.09008; found: 294.08991.

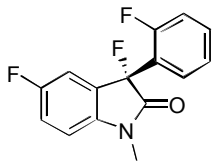
(*R*)-3-Fluoro-5-methoxy-1-methyl-3-(2-fluorophenyl)-indolin-2-one (6f). 50 °C, yellow oil, 82% yield. $[\alpha]^{27}_{D}$ = -29.9 (c = 1.05, CH_2Cl_2), 99% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 8.64 min (minor) and 10.76 min (major)]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ =7.74 (t, *J* = 7.5 Hz, 1H), 7.32-7.27 (m, 1H), 7.21 (d, *J* = 5.8 Hz, 1H), 6.94-6.85 (m, 2H), 6.77-6.74 (m, 2H), 3.67 (s, 3H), 3.21 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 171.64, 160.38, 157.92, 156.99, 138.35, 131.21, 131.13, 127.55, 127.52, 127.44, 127.41, 124.89, 116.53, 116.50, 116.44, 116.24, 112.89, 109.81, 92.91, 90.97, 56.34, 27.11. ^{19}F NMR ($CDCl_3$, 376 MHz): -114.33, -159.50. HRMS (ESI): *m/z* : calcd for $C_{16}H_{13}F_2NNaO_2$ $[M+Na]^+$: 312.08066; found: 312.08061.

(*S*)-3-Fluoro-5-methoxy-1-methyl-3-(2-trifluoromethylphenyl)-indolin-2-one (6g). 50 °C, colorless oil, 85% yield. $[\alpha]^{27}_{D}$ = -13.65 (c = 1.65, CH_2Cl_2), 98% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 8.07 min (minor) and 9.71 min (major)]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.82-7.72 (m, 2H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 6.93-6.90 (m, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.70 (s, 1H), 3.70 (s, 3H), 3.23 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 171.51, 171.33, 156.42, 156.40, 132.10, 129.16, 128.12, 127.98, 127.80, 127.75, 124.74, 122.48, 116.28, 116.25, 112.91, 109.40, 109.38, 94.26, 92.79, 55.88, 26.58. ^{19}F NMR ($CDCl_3$, 376 MHz): -57.74, -168.74. HRMS (ESI): *m/z* : calcd for $C_{17}H_{13}F_4NNaO_2$ $[M+Na]^+$: 362.07746; found: 362.07727.

(*S*)-3,5-difluoro-1-methyl-3-phenyl-indolin-2-one (6h). Room temperature, white solid, 70% yield. $[\alpha]^{27}_{D}$ = 111.8 (c = 1.25, CH_2Cl_2), 96% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 0.7 mL/min, t_R = 11.09 min (minor) and 14.93 min (major)].)]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (br, 5H), 7.15-7.05 (m, 2H), 6.84 (dd, *J* = 8.5, 2.9 Hz, 1H), 3.19 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 172.51, 172.32, 160.71, 160.69, 158.78, 158.76, 140.80, 140.79, 140.76, 140.74, 135.67, 135.45, 129.73, 129.72, 128.95, 128.57, 128.51, 128.43, 128.37, 126.02, 125.97, 118.23, 118.21, 118.04, 118.02, 114.58, 114.38, 109.92, 109.91, 109.85, 94.07, 94.06, 92.57, 92.56, 26.91. ^{19}F NMR

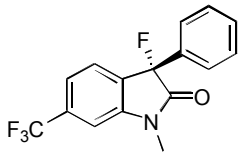
($CDCl_3$, 376 MHz): -118.73, -153.62. HRMS (ESI): *m/z* : calcd for $C_{15}H_{11}F_2NNaO$ $[M+Na]^+$: 282.07009; found: 282.07005.

(*R*)-3,5-difluoro-1-methyl-3-(2-fluorophenyl)-indolin-2-one (6i). Room



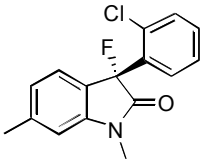
temperature, colorless oil, 76% yield. $[\alpha]^{27}_D$ = -119.84 (c = 1.90, CH_2Cl_2), 99.9% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 9.21 min (major) and 11.17 min (minor)]. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.78 (td, *J* = 7.7, 1.6 Hz, 1H), 7.39-7.34 (m, 1H), 7.29-7.25 (m, 1H), 7.09 (tt, J = 8.8, 2.3 Hz, 1H), 6.99-6.92 (m, 2H), 6.85-6.82 (m, 1H), 3.27 (s, 3H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 171.73, 171.56, 160.99, 160.10, 160.06, 159.06, 159.03, 158.13, 158.09, 141.11, 131.58, 131.52, 128.42, 128.35, 128.27, 128.21, 127.57, 127.55, 127.48, 127.46, 125.16, 125.15, 125.13, 124.51, 124.41, 124.28, 124.18, 118.60, 118.57, 118.41, 118.38, 116.55, 116.53, 116.38, 116.37, 114.12, 113.92, 110.19, 110.13, 92.26, 90.76, 27.26. ^{19}F NMR ($CDCl_3$, 376 MHz): -114.51, -119.16, -160.07. HRMS (ESI): *m/z* : calcd for $C_{15}H_{10}F_3NNaO$ $[M+Na]^+$: 300.06067; found: 300.06069.

(*R*)-3-fluoro-1-methyl-6-trifluoromethyl-3-phenyl-indolin-2-one (6j). Room



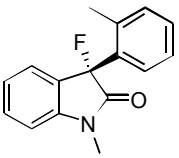
temperature, white solid, 81% yield. $[\alpha]^{27}_D$ = 108.1 (c = 2.05, CH_2Cl_2), 94% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 7.04 min (minor) and 10.56 min (major)]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45-7.34 (m, 7H), 7.12 (s, 1H), 3.25 (s, 3H). ^{13}C $\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 172.39, 172.20, 145.57, 145.53, 135.31, 135.10, 134.16, 134.14, 133.90, 133.88, 130.78, 130.77, 130.63, 130.62, 129.91, 129.89, 129.03, 126.77, 126.76, 126.04, 125.99, 124.88, 122.72, 122.71, 120.91, 120.89, 120.87, 120.85, 106.01, 106.00, 105.98, 105.97, 93.52, 92.02, 26.96. ^{19}F NMR ($CDCl_3$, 376 MHz): -62.92, -154.29. HRMS (ESI): *m/z* : calcd for $C_{16}H_{11}F_4NNaO$ $[M+Na]^+$: 332.06690; found: 332.06707.

(*R*)-3-fluoro-1,6-dimethyl-3-(2-chlorophenyl)-indolin-2-one



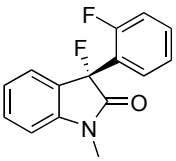
(6k). 60 °C, white solid, 86% yield. $[\alpha]^{25}_{D}$ = -96.8 (c = 1.45, CH_2Cl_2), 82% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 7.45 min (minor) and 9.22 min (major)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.29-7.20 (m, 2H), 6.87 (dd, *J* = 7.5, 2.7 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.67 (s, 1H), 3.22 (s, 3H), 2.35 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 171.89, 171.67, 146.18, 146.12, 142.98, 142.94, 135.15, 134.87, 130.77, 130.75, 130.54, 128.16, 128.01, 127.48, 127.46, 125.48, 125.46, 124.27, 124.23, 123.57, 123.39, 110.22, 110.20, 94.01, 92.20, 27.04, 22.65, 22.63. ^{19}F NMR ($CDCl_3$, 376 MHz): -152.35. HRMS (ESI): *m/z* : calcd for $C_{16}H_{13}ClFNNaO$ $[M+Na]^+$: 312.05619; found: 305.05614.

(*S*)-3-fluoro-1-methyl-3-(2-methylphenyl)-indolin-2-one (6l). Room temperature,



white solid, 59% yield. $[\alpha]^{27}_{D}$ = -23.8 (c = 1.20, CH_2Cl_2), 96% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 7.35 min (minor) and 8.94 min (major)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.1 Hz, 1H), 7.45 (tt, *J* = 7.8, 1.4 Hz, 1H), 7.34-7.28 (m, 2H), 7.18-7.14 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 3.31 (s, 3H), 1.98 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 172.01, 171.83, 144.77, 144.73, 134.59, 134.56, 134.31, 134.12, 131.67, 131.65, 131.63, 131.60, 128.91, 128.90, 126.76, 126.61, 126.02, 126.00, 125.94, 125.83, 125.77, 125.75, 123.65, 123.63, 108.76, 108.74, 94.46, 93.01, 26.47, 19.43. ^{19}F NMR ($CDCl_3$, 376 MHz): -151.65. HRMS (ESI): *m/z* : calcd for $C_{16}H_{14}FNNaO$ $[M+Na]^+$: 278.09516; found: 278.09497.

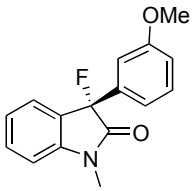
(*R*)-3-fluoro-1-methyl-3-(2-fluorophenyl)-indolin-2-one (6m). Room temperature,



white solid, 65% yield. $[\alpha]^{27}_{D}$ = -101.5 (c = 0.85, CH_2Cl_2), 99.3% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 7.72 min (minor) and 9.16 min (major)]. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* =7.74 (td, *J* = 7.6, 1.6 Hz, 1H), 7.41-7.31 (m, 2H), 7.27 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.18 (d, 7.8 Hz, 1H), 7.03 (t, 7.6 Hz, 1H), 6.97-6.88 (m, 2H), 3.27 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 171.49, 171.28, 159.79, 159.73, 157.33, 157.27, 144.60, 144.55, 131.65, 131.62, 130.68, 130.60, 127.07, 127.04, 126.96, 126.93,

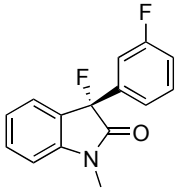
126.57, 126.38, 125.27, 124.56, 124.43, 124.40, 123.38, 123.35, 115.91, 115.89, 115.70, 108.82, 92.05, 90.19, 26.54. ^{19}F NMR ($CDCl_3$, 376 MHz): -114.47, -159.50. HRMS (ESI): *m/z* : calcd for $C_{15}H_{11}F_2NNaO$ $[M+Na]^+$: 282.07099; found: 282.07042.

(*S*)-3-fluoro-1-methyl-3-(3-methoxyphenyl)-indolin-2-one (6n). Room



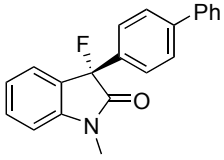
temperature, colorless oil, 50% yield. $[\alpha]^{27}_D$ = 94.7 (c = 0.95, CH_2Cl_2), 95% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 8.74 min (minor) and 9.40 min (major)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (tt, *J* = 7.8, 1.6 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 8.2 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 1.9 Hz, 1H), 6.86-6.81 (m, 3H), 3.75 (s, 3H), 3.16 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 172.67, 172.48, 159.97, 144.88, 144.84, 137.74, 137.53, 131.82, 131.80, 128.89, 127.15, 127.01, 126.36, 123.84, 123.82, 118.39, 118.35, 115.03, 111.93, 111.88, 109.10, 94.16, 92.66, 55.60, 26.77. ^{19}F NMR ($CDCl_3$, 376 MHz): -153.42. HRMS (ESI): *m/z* : calcd for $C_{16}H_{14}FNNaO_2$ $[M+Na]^+$: 294.09008; found: 294.09014.

(*S*)-3-fluoro-1-methyl-3-(3-fluorophenyl)-indolin-2-one (6o). Room temperature,



white solid, 80% yield. $[\alpha]^{25}_D$ = 106.1 (c = 1.85, CH_2Cl_2), 96% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min, t_R = 6.62 min (minor) and 7.24 min (major)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (t, *J* = 7.8 Hz, 1H), 7.34-7.30 (m, 2H), 7.15-7.03 (m, 4H), 6.92 (d, *J* = 7.9 Hz, 1H), 3.21 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 172.24, 172.05, 163.99, 162.03, 144.91, 144.87, 138.73, 138.67, 138.51, 138.45, 132.12, 132.10, 130.56, 130.50, 126.67, 126.52, 126.39, 126.38, 124.01, 123.99, 121.91, 121.89, 121.87, 121.84, 116.62, 116.61, 116.45, 116.44, 113.77, 113.71, 113.58, 113.52, 109.28, 109.27, 93.73, 93.71, 92.22, 92.21, 26.84. ^{19}F NMR ($CDCl_3$, 376 MHz): -111.93, -153.07. HRMS (ESI): *m/z* : calcd for $C_{15}H_{11}F_2NNaO$ $[M+Na]^+$: 282.07009; found: 282.06984.

(*S*)-3-fluoro-1-methyl-3-(4-biphenyl)-indolin-2-one (6p). Room temperature, white solid, 61% yield. $[\alpha]^{27}_D$ = 116.6 (c = 0.90, CH_2Cl_2), 94% ee [Chiralcel OJ-H column, *n*-hexane/*i*-PrOH =80:20, 1.0 mL/min, t_R = 27.34 min (minor) and 30.65 min (major)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59-7.54 (m, 4H), 7.47-7.32 (m, 7H),



7.16 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 3.23 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 172.79, 172.60, 144.96, 144.91, 142.52, 142.50, 140.71, 135.10, 134.89, 131.90, 131.87, 129.10, 127.89, 127.64, 127.63, 127.46, 127.05, 126.90, 126.80, 126.75, 126.49, 123.89, 123.87, 109.18, 109.17, 94.16, 92.67, 26.81. ^{19}F NMR ($CDCl_3$, 376 MHz): -152.25. HRMS (ESI): *m/z* : calcd for $C_{21}H_{16}FNNaO$ $[M+Na]^+$: 340.11081; found: 340.11090.

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Chapter 4

Monodentate N-Heterocyclic Carbene (NHC) - Copper Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Grignard Reagents

Wu, L.; Ou, A.; Salvador, A.; Linden, A.; Dorta, R. *To be submitted*.

4.1 Abstract

A new NHC·Cu catalyzed asymmetric ring-opening of oxabicyclic alkenes with Grignard reagents is reported. Based on the chiral regime of C_2-symmetric starting diamines, the naphthyl-based chiral NHC ligands were readily prepared (Chapter 3). When the 2-positions of the naphthyl side chains were substituted with cyclooctyl groups, only one diastereomer was generated in the corresponding NHC salt. The enantiopure NHC ligand was then transferred onto a copper complex, which was tested in the asymmetric ring-opening of oxabicyclic alkenes with Grignard reagents. The ring-opened products were obtained in high yields, high enantioselectivities and excellent *trans* diastereoselectivities. When phenyl or allyl Grignard reagents were used, high yields and moderate selectivities were observed.

4.2 Introduction

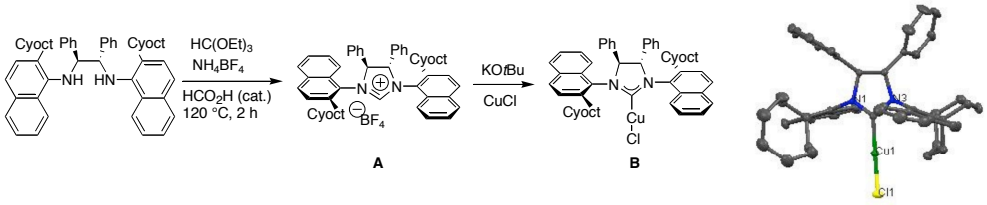
Transition-metal-catalyzed asymmetric C-C bond-formation reactions which employ organometallic reagents are of the most useful and practical methods in organic synthesis. The enantioselective ring opening of *meso*-oxabicyclic alkenes with organometallic reagents is an efficient method to construct cyclic compounds with multiple chiral centers while simultaneously generating a new C-C bond.[1] Following the pioneering work of Lautens *et al.*, this asymmetric transformation has been accomplished successfully with various organometallic reagents, such as organozinc,[2] organoaluminum,[3] organoboron,[4] Grignard reagent,[3c, 5] and recently organolithium[6] in the presence of palladium, nickel, rhodium and copper catalysts. In all of these cases, enantioselectivity arrises by choosing the appropriate chiral phosphine or phosphoramidite ligands. Chiral *N*-heterocyclic carbenes as ancillary ligands have so far not been reported in these reaction schemes.

Due to their versatility, tunable steric and electronic properties, and ease of formation of stable metal complexes, NHCs have found extensive utility in transition metal catalysed,[7] and organocatalytic,[8] reactions. Chiral NHC ligands are slow to make their way into the realm of asymmetric catalytic reactions that provide products with high asymmetric induction. Moreover, development of chiral monodentate NHC ligands that induce high selectivity in asymmetric organometallic catalysis is still at an early stage with relatively few reports detailing high enantioselectivities.[9] The

main difficulties in designing efficient ligands of this type reside in placing stereocontrol elements at positions close to the metal center without affecting the overall reactivity of the catalysts. Our group has reported the synthesis of new NHC ligands with a chiral *N*-heterocycle and naphthyl side chains. In principle, three different isomers exist in such monodentate chiral imidazolinium salts.[10] Recently, we were able to exclusively access one of these diastereomers in pure form (salt **A**, Scheme 1) by introducing cyclooctyl groups to the 2-positions of the naphthyl side chains. Its palladium complex showed excellent enantioinduction in the α-arylation of amides forming 3-fluoro-3-aryl oxindoles.[9r]

The nearly perfect C_2-symmetry of this ligand creates a remarkable chiral environment around the metal center and we therefore envisioned that this particular ligand would have potential applications in other transition metal catalyzed reactions. Here, we report the synthesis of a copper complex of this ligand (**B**) and its application in asymmetric ring opening of oxabicyclic alkenes with Grignard reagents. Good reactivities (up to 92% yield) and high enantioselectivities (up to 92% ee) were obtained.

4.3 Results and Discussion



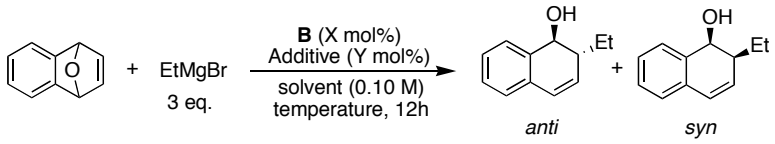
Scheme 1. Synthesis of a copper-NHC* complex (**B**) and its solid state structure

The NHC salt **A** was obtained as a single diastereomer according to our previously reported procedure.[9r] Copper complex **B** was subsequently synthesized by deprotonation of salt **A** followed by complexation with CuCl. Appropriate workup gave compound **B** as a bench-stable white solid whose structure was unambiguously confirmed by single-crystal X-ray crystallography (Scheme 1). As can be seen from the crystal structure, the backbone atoms deviate measurably from the plane of three ring atoms. The NHC ligand shows perfect C_2-symmetry and the ligand-Cu-Cl adopted a linear conformation.

With precatalyst **B** in hand, we started our investigation by optimizing different

reaction conditions. Without any additives, 5 mol% of complex promoted this transformation with high conversion at -20 °C after 3 days by using dichloroethane (DCE) as the solvent. However, the diastereoselectivity and enantioselectivity were moderate (Table 1, entry 1). Fortunately, the addition of NaBArF (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) significantly enhanced the enantioselectivity to 83% ee and the *anti* isomer was highly favored (entry 2), although the conversion was sluggish after 12 h. Adding silver salts had a negative effect on the reactivity and only trace product was observed (entries 3 and 4). Interestingly, increasing the temperature will enhance both the enantioselectivity and reactivity while

Table 1. Optimization of the reaction conditions.



entry	X	additive (Y)	solvent	T (°C)	conv. (%)[a]	anti/syn[b]	ee (%)[c]
1[d]	5	----	DCE	-20	95	5:1	47
2[e]	5	NaBArF (10)	DCE	-20	50	>99:1	83
3	5	$AgPF_6$ (10)	DCE	-20	10	----	----
4	5	$AgBF_4$ (10)	DCE	-20	5	----	----
5[f]	5	$NaBF_4$	DCE	RT	100	----	----
6	5	$NaBPh_4$	DCE	RT	100	>99:1	71
7	5	NaBArF (10)	DCE	0	100	>99:1	88
8	5	NaBArF (10)	DCE	RT	100	>99:1	92
9[e,g]	1	NaBArF (2)	DCE	RT	100	5:1	84
10[e,g]	0.5	NaBArF (1)	DCE	RT	100	1.2:1	81
11[e,g]	0.2	NaBArF (0.4)	DCE	RT	100	1:3	80
12[h]	0.005	NaBArF (0.01)	DCE	70	100	1:35	36
13	5	NaBArF (7)	DCE	RT	100	>99:1	92
14[e]	5	NaBArF (7)	Benzene	RT	100	>99:1	83
15	5	NaBArF (7)	THF	RT	5	----	----
16	5	NaBArF (7)	DCM	RT	100	60:1	83
17[i]	5	NaBArF (7)	Hexane	RT	100	>99:1	90

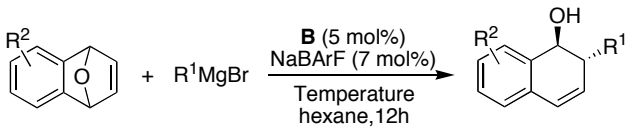
[a] determined by ^{1}H NMR and/or GC-MS. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. Isolated cis isomer is racemic. [d] 72h. [e] 15-20% of dehydroxylation product 2-ethylnaphthalene was observed. [f] full conversion to 2-ethylnaphthalene [g] 60h. [h] 90% of naphthalene was observed.

maintaining the diastereoselectivity. Moreover, 92% ee could be obtained at room

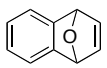
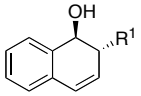
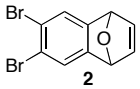
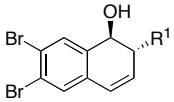
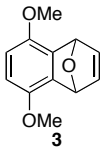
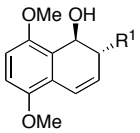
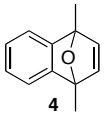
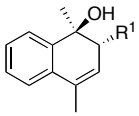
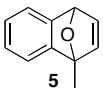
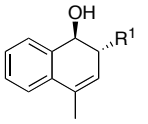
temperature using DCE as the solvent (entry 8). Using $NaBF_4$ as the additive at room temperature led to full conversion to the by-product 2-ethylnaphthalene (entry 5). $NaBPh_4$, the non-fluorinated analogue of NaBArF, promoted the reaction efficiently but with lower enantioselectivity (entry 6). When we tried to decrease the catalyst loading, the *syn*-product was found to be preferable and the enantioselectivity decreased along with decomposition of either the product (entries 9-11) or the starting material (entry 12). The amount of NaBArF additive could be lowered to 7% without affecting the selectivity and reactivity (entry 13). Switching to THF as the reaction solvent will completely shut down the reaction (entry 15). Interestingly, using hexane as the solvent will give a clean outcome with excellent selectivities and reactivity (entry 17).

To evaluate the scope of this reaction, various oxabenzonorbornadienes and Grignard reagents were studied and are listed in Table 2. In most cases, full conversion was achieved after stirring the reaction mixture for 12 h at room temperature or 50 °C and the *anti* products were formed exclusively. A broad range of primary Grignard reagents reacted with oxabenzonorbornadiene forming the products with good reactivities and enantioselectivies (entries 1-7). The bromo Grignard reagent is superior to the chloro counterpart in terms of enantioselectivity (entries 3 and 4). Furthermore, the use of secondary Grignard reagent isopropylmagnesium bromide leads to good yields, although the selectivity is moderate (entry 8). Performing the reaction of 6,7-dibromo-substituted oxabenzonorbornadiene (**2**) and isobutylmagnesium bromide at room temperature afforded good reactivity and selectivity (entry 9). With slight heating, the yield of the product could be improved to 91% and the enantioselectivity decreased only slightly (entry 10). The reaction of bulky substrate **3**, which contains methoxy groups at the 5,8-positions, gave moderate selectivity (entry 11). Substrate **4**, which bears two methyl groups at the 1,4-positions, reacts with different primary Grignard reagents efficiently at room temperature affording the products with good selectivities (entries 12-14). For unsymmetrical oxabenzonorbornadiene **5** bearing a methyl substituent at the bridgehead position, the expected kinetic resolution of the racemic substrate with EtMgBr was not observed and the *anti* ring opened product **6l** was obtained with only 9% ee in a yield of 65% (entry 15). The reaction proceeded with complete regioselectivity by attack of the ethyl Grignard reagent onto the olefinic terminus distant to the methyl group.

Table 2. Asymmetric ring opening of oxabenzonorbornadienes with alkyl Grignard reagents[a]



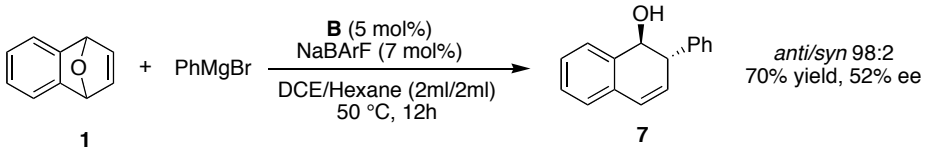
anti:*syn* >99:1

entry	substrate	T (°C)	R^1	product		yield (%)[b]	ee (%)[c]
1[d]	 **1**	RT	Et		**6a**	85	92
2		RT	Me		**6b**	76	75
3		RT	*n*Bu		**6c**	90	87
4[e]		50	*n*Bu		**6c**	92	74
5		50	*i*Bu		**6d**	92	88
6[d]		RT	*i*Bu		**6d**	30	91
7		RT	$nC_{12}H_{25}$		**6e**	71	74
8		50	*i*Pr		**6f**	92	52
9	 **2**	RT	*i*Bu		**6g**	83	85
10		50	*i*Bu		**6g**	91	80
11	 **3**	RT	Et		**6h**	81	47
12	 **4**	RT	Et		**6i**	88	84
13		RT	*n*Pent		**6j**	86	77
14		RT	*i*Bu		**6k**	86	88
15	 **5**	RT	Et		**6l**	65	9

[a] reaction conditions: oxabenzonorbornadiene (0.2 mmol), R^1MgBr (3.0 eq.), **B** (5 mol%), NaBArF (7 mol%). [b] Isolated yield. In all cases *anti*/*syn* are >99/1. [c] ee of trans product and determined by chiral HPLC. [d] DCE (3 ml) was used as solvent [e] *n*BuMgCl was used as the Grignard reagent.

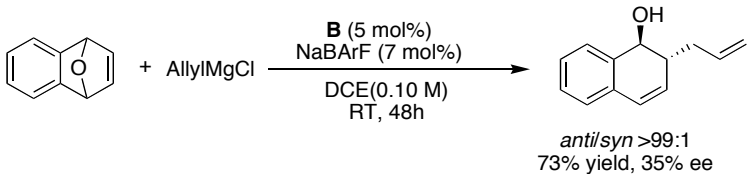
To the best of our knowledge, there is only one report to date describing the asymmetric desymmetrization of oxabenzonorbornadienes with aryl groups giving the *anti* product. In 2009, Alexakis *et al.* used $PhAlEt_2$ as the arylation agent to get the corrresponding product **7** with 84% ee. However, due to the competing reaction

between phenyl and ethyl groups of $PhAlEt_2$, the yield was low (40%). In our preliminary trial, we were delighted to find that our catalyst promotes the reaction between oxabenzonorbornadiene and phenylmagnesium bromide smoothly, providing the product with 70% yield albeit with moderate selectivity (Scheme 2). Further studies are in progress towards the improvement of enantioselectivity in this asymmetric transformation.



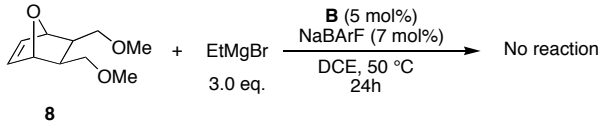
Scheme 2. Ring opening of oxabenzonorbornadiene with phenylmagnesium bromide

Allyl magnesium halides are another class of nucleophiles that in general do not show any reactivity in these transformations.[5b] We found that, by using copper complex **B** as the precatalyst, the asymmetric ring-opening of oxabenzonorbornadiene with allyl magnesium chloride leads to the *anti* product in a good 73% yield although with only very moderate enantioselectivity (35% ee, Scheme 3).



Scheme 3. Ring opening of oxabenzonorbornadiene with allylmagnesium chloride

Finally, the less reactive non-aromatic oxabicyclic alkene, 5,6-bismethoxymethyl-7-oxa-bicyclo[2.2.1]-2-heptene, was also examined in the reaction with ethyl magnesium bromide. Only the starting material was recovered under our reaction conditions (50 °C, one day) (**Scheme 4**).



Scheme 4. Trial of ring-opening of oxabicyclic alkene **8**

4.4 Conclusion

In summary, we have developed the first chiral NHC-copper catalyst that effects

the enantioselective ring-opening of oxabicyclic alkenes with Grignard reagents. The ring-opened products were obtained in high yields, high enantioselectivities and excellent *trans* diastereoselectivities. Other asymmetric transformations using this catalyst are underway.

Acknowledgment. Support for this work was provided by the SNF (grant to L. Wu), the University of Zurich and the University of Western Australia.

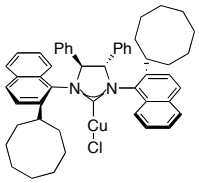
4.5 Experimental Part

General: All reactions were carried out using standard Schlenk or glovebox (Mecaplex or Innovative Technology) techniques under nitrogen. All reagents were used as received unless otherwise noted. Solvents were purchased in the best quality available, degassed by purging thoroughly with nitrogen and dried over molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Solvents for NMR spectroscopy were degassed with nitrogen and dried over molecular sieves. NMR spectra were collected on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra were calibrated to the residual 1H and 13C of the solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). High-resolution electrospray ionization mass spectrometry was performed on a *FinniganMAT 900* (Finnigan MAT95, San Jose, CA; USA) double-focusing magnetic sector mass spectrometer (geometry BE). GC-MS analysis was done on a Finnigan Voyager GC8000 Top. X-ray crystallography was performed on an *Agilent Technologies SuperNova* area-detector diffractometer using Mo *K*α radiation (λ = 0.71073 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler.

Chiral NHC salt **A** was prepared according to our previous report. [9r]

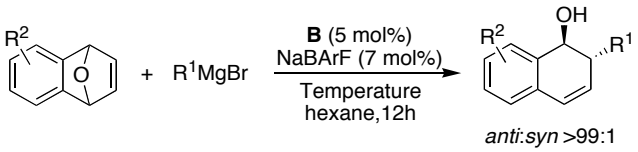
Oxabenzonorbornadienes **2**,[11] **3**,[12] **4**,[13] **5**,[14] and **8**[3b] were prepared according to literature.

Synthesis of Cu complex B:



Chloro [*4S*,*5S*-*1*,3-Bis(2-cycoctyl-naphthalen-1-yl)-4,5-dihydro-4,5-diphenyl imidazol-2-ylidene] copper (I) [((*2*)-DiPhSICyoctNap)CuCl]. A (1.50 g, 1.92 mmol), KO*t*Bu (279 mg, 2.49 mmol) and CuCl (247 mg, 2.49 mmol) were mixed together in a round flask in the glovebox. Dry THF (30 mL) was added and the mixture was stirred at room temperature for 4 h. The resulting mixture was filtered through celite and dried under vacuum, and the residue was further purified by flash chromatography on siliga gel (DCM:ethanol 100:1) to afford the title product as a white solid (900 mg, 59%). Elemental analysis: calcd for $C_{51}H_{54}ClN_2Cu$: C, 77.15; H, 6.86; N, 3.53. Found: C, 76.80; H, 6.81; N, 3.22. $[\alpha]^{25}_D$ = -144.5 (c = 0.77, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.13 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.1 Hz, 2H), 7.76-7.72 (m, 4H), 7.53 (t, J = 7.5 Hz, 2H), 7.23-7.07 (m, 12H), 6.12 (s, 2H), 3.12 (br, 2H), 2.06-2.05 (m, 2H), 1.72-1.60(m, 24H), 0.32-0.28 (m, 2H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 203.78, 148.67, 134.06, 133.72, 131.22, 130.52, 130.02, 129.95, 129.75, 129.50, 129.30, 128.08, 126.34, 125.96, 122.79, 73.49, 40.33, 36.74, 34.20, 28.21, 27.85, 27.00, 26.60, 26.26. HRMS (ESI): *m/z* : calcd for $C_{51}H_{54}ClN_2CuNa$ $[M+Na]^+$: 815.31637; found: 815.31582.

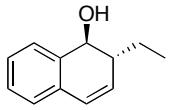
Catalytic ring-opening reaction:



General catalysis procedure: A solution of copper complex **B** (7.9 mg, 0.010 mmol), and NaBArF (12.8 mg, 0.014 mmol) in anhydrous hexane (6 mL) or DCE (3 ml) was stirred at room temperature for 15 min. Oxabenzonorbornadiene (0.20 mmol) was added to this colorless solution followed by the addition of the Grignard reagent in diethyl ether. The solution was stirred at the corresponding temperature for 12h. After quenching with an aqueous solution of Na_2CO_3 (1.0 M, 1 mL) at -20 degree, the reaction mixture was extracted with ether (3 X 10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to give a crude product, which was

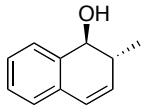
subjected to flash chromatography on silica gel with n-hexane/ethyl acetate/triethyl amine (100:15:1) to afford the product. The enantiomeric excess of the product was analyzed by HPLC.

(-)-*trans*-2-Ethyl-1,2-dihydronaphth-1-ol (6a, Table 2, entry 1)



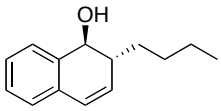
85% yield, colorless oil, the spectral data were in accordance with those reported in the literature.[2c] 92% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =98:2, 1.0 mL/min; *t* = 18.1 min (major) and 21.2 min (minor)].

(-)-*trans*-2-Methyl-1,2-dihydronaphth-1-ol (6b, Table 2, entry 2)



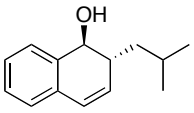
76% yield, white solid, the spectral data were in accordance with those reported in the literature. [2c] 75% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 33.2 min (major) and 37.8 min (minor)].

(-)-trans-2-*n*-Butyl-1,2-dihydronaphth-1-ol (6c, Table 2, entry 3)



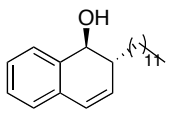
90% yield, white solid, the spectral data were in accordance with those reported in the literature. [2c] 87% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 26.9 min (major) and 34.1 min (minor)].

(-)-trans-2-*iso*-Butyl-1,2-dihydronaphth-1-ol (6d, Table 2, entry 5)



92% yield, white solid, the spectral data were in accordance with those reported in the literature. [15] 88% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 25.2 min (major) and 31.7 min (minor)].

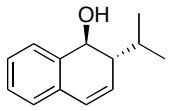
(-)-trans-2-*n*-Dodecyl-1,2-dihydronaphth-1-ol (6e, Table 2, entry 7)



71% yield, white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27 (d, *J* = 7.1 Hz, 1H), 7.19-7.14 (m, 2H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.40 (d, *J* = 10,6 Hz, 1H), 5.93 (t, *J* = 5.1 Hz, 1H), 4.43 (s, 1H), 2.47 (br, 1H), 1.31-1.67 (m, 22H), 0.81-0.79 (m, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 136.32, 132.97, 131.70, 129.08, 128.46, 128.20, 127.08, 126.46, 73.05, 43.13, 32.52, 32.22, 30.40, 30.27,

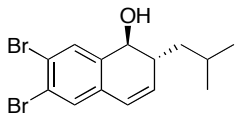
30.24, 30.21, 30.13, 29.95, 27.71, 23.29, 14.71. HRMS (EI): *m/z* : calcd for $C_{22}H_{34}O$ $[M]^+$: 314.26042; found: 314.26092. $[\alpha]^{25}_D$ = -163.4 (c = 0.97, CH_2Cl_2), 74% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 19.2 min (major) and 24.8 min (minor)].

(-)-trans-2-*iso*-Propyl-1,2-dihydronaphth-1-ol (6f, Table 2, entry 8)



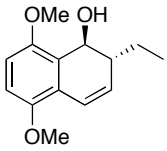
92% yield, white solid, the spectral data were in accordance with those reported in the literature. [2c] 52% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 27.6 min (major) and 37.8 min (minor)].

(-)-*trans*-2-*iso*-Butyl-6,7-dibromo-1,2-dihydronaphth-1-ol (6g, Table 2, entry 10)



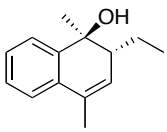
91% yield, colorless oil, the spectral data were in accordance with those reported in the literature. [5b] 80% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 31.6 min (major) and 39.2 min (minor)].

(-)-*trans*-2-Ethyl-5,8-dimethoxy-1,2-dihydronaphth-1-ol (6h, Table 2, entry 11)



81% yield, colorless oil, the spectral data were in accordance with those reported in the literature. [2c] 47% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min; *t* = 14.0 min (minor) and 27.1 min (major)].

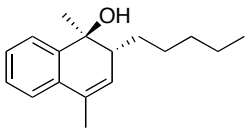
(-)-*trans*-2-Ethyl-1,4-dimethyl-1,2-dihydronaphth-1-ol (6i, Table 2, entry 12)



88% yield, colorless oil, the spectral data were in accordance with those reported in the literature. [2c] 84% ee [Chiralpak AD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 19.2 min (major) and 30.4 min (minor)].

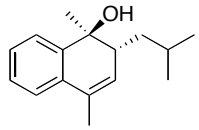
(-)-*trans*-2-*n*-Pentyl-1,4-dimethyl-1,2-dihydronaphth-1-ol (6j, Table 2, entry 13)

86% yield, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60-7.58 (m, 1H), 7.26-7.22 (m, 3H), 5.71 (dd, *J* = 2.9, 1.5Hz, 1H), 2.34-2.32 (m, 1H), 2.06 (t, *J* = 1.8 Hz,



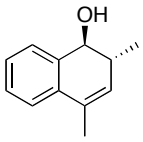
3H), 1.75-1.71 (m, 1H), 1.51-1.20 (m, 11H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 144.31, 134.63, 131.96, 129.01, 128.30, 127.83, 123.85, 123.73, 75.28, 47.30, 32.68, 28.73, 27.93, 23.26, 23.07, 19.73, 14.69. HRMS (ESI): *m/z* : calcd for $C_{17}H_{24}O$ $[M]^+$: 244.18217; found: 244.18230. $[\alpha]^{25}_D$ = -47.60 (c = 1.37, CH_2Cl_2), 77% ee [Chiralpak AD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 15.3 min (major) and 23.8 min (minor)].

(-)-*trans*-2-*iso*-Butyl-1,4-dimethyl-1,2-dihydronaphth-1-ol (6k, Table 2, entry 14)



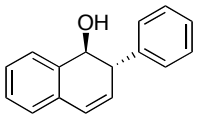
86% yield, colorless oil, the spectral data were in accordance with those reported in the literature.[5b] 88% ee [Chiralpak AD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; *t* = 13.4 min (major) and 15.9 min (minor)].

(-)-*trans*-2-Ethyl-4-methyl-1,2-dihydronaphth-1-ol (6l, Table 2, entry 15)



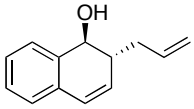
65% yield, colorless oil, the spectral data were in accordance with those reported in the literature. [2c] 9% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =99:1, 0.5 mL/min; *t* = 55.3 min (major) and 59.1 min (minor)].

(-)-*trans*-2-Phenyl-1,2-dihydronaphth-1-ol (6m, Scheme 2)



70% yield, white solid, the spectral data were in accordance with those reported in the literature.[15] 7.45 (dd, J = 7.2, 0.8 Hz, 1H), 7.35-7.29 (m, 7H), 7.22 (dd, J = 7.0, 1.7 Hz, 1H), 6.70 (dd, J = 9.6, 2.0 Hz, 1H), 6.08 (dd, J = 9.6, 3.8 Hz, 1H), 4.88 (dd, J = 7.7, 5.2 Hz, 1H), 3.86-3.83 (m, 1H), 1.99 (d, J = 5.3 Hz, 1H). ^{13}C NMR 140.87, 135.60, 132.59, 129.82, 128.79, 128.42, 128.25, 128.10, 127.65, 127.21, 126.41, 74.36, 50.16. $[\alpha]^{25}_D$ = -144.4 (c = 0.93, CH_2Cl_2), 52% ee [Chiralcel OJ-H column, *n*-hexane/*i*-PrOH =90:10, 1.0 mL/min; *t* = 12.7 min (major) and 22.2 min (minor)].

(-)-*trans*-2-Allyl-1,2-dihydronaphth-1-ol (6n, Scheme 3)



73% yield, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38-7.27 (m, 3H), 7.17 (dd, J = 7.1, 1.2 Hz, 1H), 6.07-5.98 (m, 1H), 5.88 (dd, J = 8.1, 1.5 Hz, 1H), 5.25-5.15 (m, 2H), 4.64 (s, 1H), 2.63-2.59 (m, 2H), 2.45-2.36 (m, 1H), 1.64 (d, J = 6.5 Hz, 1H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): 136.66, 136.59, 132.64, 130.29, 128.61, 127.70, 127.61, 127.03, 126.59, 116.88, 70.26, 40.31, 33.62. HRMS (EI): *m/z* : calcd for $C_{13}H_{14}O$ $[M]^+$: 186.10392; found: 186.10378. $[\alpha]^{25}_D$ = -55.64 (c = 0.63, CH_2Cl_2), 35% ee [Chiralcel OD-H column, *n*-hexane/*i*-PrOH =99:1, 1.0 mL/min; t = 24.3 min (major) and 27.6 min (minor)].

4.6 References and Notes

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Chapter 5

Monodentate Chiral N-Heterocyclic Carbene Palladium Catalyzed Asymmetric Suzuki-Miyaura and Kumada Couplings

Wu, L.; Shi, M. W.; Salvador, A.; Ou, A.; Skelton, B.; Dorta, R. *To be submitted*.

5.1 Abstract

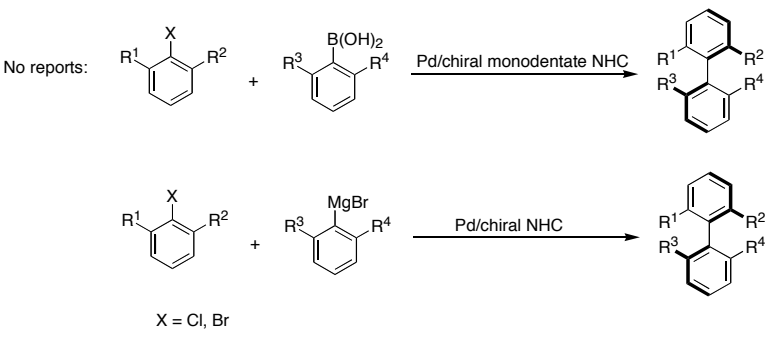
N-Heterocyclic carbene ligands derived from C_2-symmetric diamine with naphthyl side chains are introduced as chiral monodentate ligands, and their palladium complexes (NHC)Pd(cin)Cl are prepared. At the 2-position of the naphthyl moiety, a 4-heptyl group is introduced. These compounds exist as a mixture of diastereomers, and the palladium complexes can be successfully separated. When one of the pure palladium diastereomers (*Sa*,*Sa*) is used in the asymmetric Suzuki-Miyaura and Kumada coupling, chiral biaryls can be obtained in high yield and moderate selectivity.

5.2 Introduction

Axially chiral biaryls are common and decisive structure motifs in bioactive compounds[1] and are the fundamental basis for most effective chiral ligands, such as the well-known BINAP[2] and BINOL[3] ligands. Cross-coupling reactions[4] (*i.e.* Suzuki-Miyaura coupling and Kumada coupling) have opened a direct and convenient route to such unsymmetric axially chiral molecules like biaryls, which cannot be readily obtained by other catalytic asymmetric reactions. The first successful atroposelective cross-coupling was reported by Hayashi in the late 1980s using aryl halides and aryl Grignard reagents as the coupling partners (Kumada coupling) and chiral ferrocenylphosphine/Ni as the catalyst.[5] Following this seminal work, several phosphine ligands were examined in the Kumada coupling but only low to moderate enantioselectivities have been achieved to date.[6] To date, several reports of asymmetric Suzuki-Miyaura and Kumada coupling using chiral phosphine ligands have appeared.[7] The earliest reports of asymmetric cross-coupling of aryl halides and aryl boron reagents were disclosed by Cammidge[8] and Buchwald[9] using ferrocene and binaphthyl derived phosphines respectively. Since then, a variety of chiral ligands have been examined for the asymmetric Pd-catalyzed Suzuki-Miyaura coupling reaction.[10] Moreover, it is noteworthy that Uozumi reported a chiral resin-supported phosphine ligand that efficiently catalyzes the synthesis of axially chiral biaryl compounds via Suzuki-Miyaura coupling with excellent selectivities (up to 94% ee) in water.[10f] More recently, in 2008 Lassaletta *et al.* disclosed a new class of chiral bis-hydrazone ligands derived from C_2-symmetric hydrazines for the asymmetric Suzuki-

Miyaura coupling, providing the biaryls in high selectivity (up to 98% ee).[10e] In addition, Suginome showed that helically chiral poly(quinoxaline-2,3-diyl)-based phosphines serve as highly enantioselective ligand (up to 95% ee) in the Suzuki–Miyaura coupling reaction to form axially chiral biarylphosphinic esters.[10i]

N-heterocyclic carbenes (NHCs) have received a great deal of attention in the past decade and are now considered as ligands of choice for various (asymmetric) catalytic reactions.[11] The use of NHCs as ligands in cross-coupling has been intensively studied by different research groups and they have demonstrated remarkably high activity promoting this kind of transformation.[11c,12] The capacity of NHCs has been illustrated not only in cross-coupling reactions but also in different asymmetric transformations.[13] However, little attention has been given to the asymmetric cross-coupling using chiral NHCs as the ligands. To the best of our knowledge, there are only two reports to date on using chiral NHC ligands to promote asymmetric cross-coupling reactions. In 2010, Labande disclosed the first example of asymmetric Suzuki-Miyaura coupling with palladium complexes bearing chelating, planar chiral ferrocenyl phosphine-NHC ligands.[14] However, only low enantioselectivities were achieved (less than 40% ee) in this transformation using aryl bromides as the electrophiles. Recently, Zhang *et al.* prepared two palladium complexes of bis-NHC ligands derived from 1,2-cyclohexanediamine and employed them to catalyze the asymmetric Suzuki-Miyaura couplings of aryl bromides with arylboronic acids in good yields and moderate enantioselectivities (up to 61% ee).[15] As far as we are aware, there are no reports on asymmetric cross-coupling using chiral monodentate NHCs as the stereocontrolling ligand. Moreover, no chiral (monodentate or chelate) NHC ligands have been disclosed for the asymmetric Kumada cross-coupling reaction.



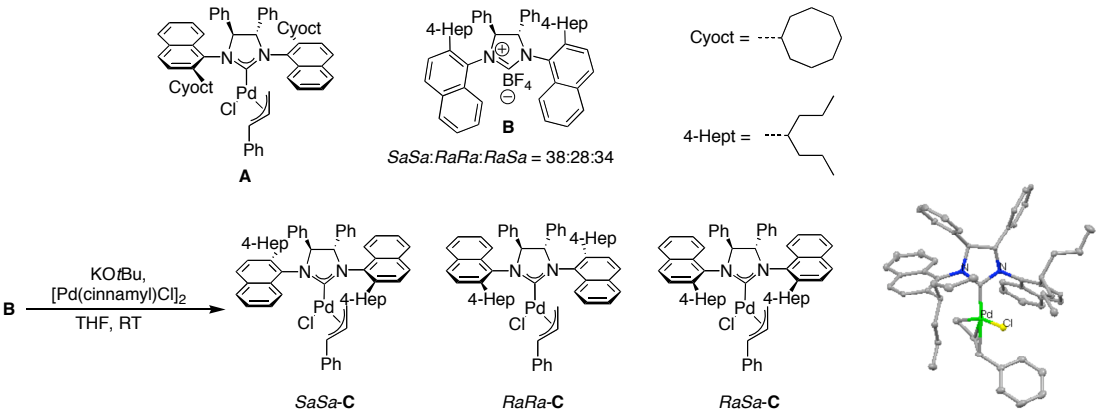
Scheme 1. Asymmetric Suzuki-Miyaura and Kumada coupling

5.3 Results and Discussion

Our group has developed a new type of monodentate NHC ligand with a chiral N-heterocycle and naphthyl side chains. These compounds exist as a mixture of diastereomers and their palladium complexes showed different selectivity asymmetric intramolecular α-arylation.[16] Recently, we have gained access to only one diastereomer by introdution of bulky cyclooctyl groups to the 2-position of the naphthyl side chain. The palladium cinnamyl complex (Scheme 1, **A**) thereof allowed the direct synthesis of 3-aryl-3-fluoro-oxindoles via an α-arylation protocol in good yields and with excellent enantioselectivities (up to >99% ee).[17]

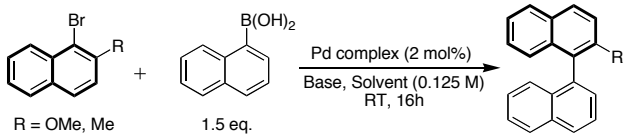
When this complex was used to catalyze the coupling between 1-bromo-2-methoxynaphthalene and 1-naphthylboronic acid (asymmetric Suzuki-Miyaura coupling), a high yield of the product was obtained. However, only low enantioselectivity (25%) was observed (entry 1, Table 1). When the bulky and acyclic 4-heptyl moiety was introduced to the 2-position of the naphthyl group, a new NHC salt (Scheme 2, **B**) was generated and a mixture of three diastereomers was observed with the ratio of 38:28:34 [(*Sa,Sa*):(*Ra,Ra*):(*Ra,Sa*)]. While the separation of these three diastereomeric salts turned out to be impossible, we successfully separated the corresponding palladium cinnamyl complexes via simple column chromatography. The structure of one of the isomers [(*Ra,Sa*)-**C**] was unambiguously confirmed by single-crystal X-ray crystallography. All of these three complexes were independently tested in the asymmetric Suzuki-Miyaura coupling. To our surprise, the (*Ra,Ra*) isomer, which showed the best enantiomeric discrimination in asymmetric α-arylations, gave low reactivity and selectivity (entry 2). In contrast, isomer (*Ra,Sa*)-**C** showed excellent reactivity in this tranformation while giving the racemic product (entry 3). Conversely, the (*Sa,Sa*)-**C** diastereomer, which possesses the alkyl chains opposite to the phenyl groups, promoted this reaction efficiently affording the tri-*ortho*-substituted biaryl in excellent yield (91%) and moderate enantioselecvitity (60% ee, entry 4). When 1-bromo-2-methylnaphthalene instead of 1-bromo-2-methoxynaphthalene was used, a slightly lower ee was observed (entry 5). Screening of the solvent revealed that toluene is the best choice and that ethereal solvents and dichloromethane gave lower enantioselectivities (entries 6-9). The catalyst showed little reactivity in hexane (entry 10). Optimization of the base revealed that NaO*t*Bu gave much lower yield and enantioselectivity compared to KO*t*Bu (entry 11), while

the use of LiO*t*Bu and KHMDS led to the recovery of the starting material (entries 12 and 13).



Scheme 1. NHC-Pd complexes tested in this study

Table 1. Optimization of the Suzuki-Miyaura reaction condition.[a]



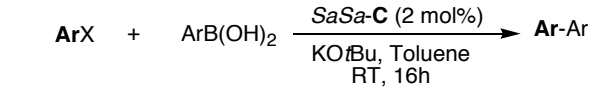
Entry	Pd complex	R	Base	Solvent	Yield[b]	e.e.[c]
1	**A**	OMe	KO*t*Bu	Toluene	90	25
2	*RaRa*-**C**	OMe	KO*t*Bu	Toluene	55	22
3	*RaSa*-**C**	OMe	KO*t*Bu	Toluene	93	8
4	*SaSa*-**C**	**OMe**	**KO*t*Bu**	**Toluene**	**91**	**60**
5	*SaSa*-**C**	**Me**	**KO*t*Bu**	**Toluene**	**94**	**51**
6	*SaSa*-**C**	Me	KO*t*Bu	THF	92	40
7	*SaSa*-**C**	Me	KO*t*Bu	DME	83	50
8	*SaSa*-**C**	Me	KO*t*Bu	Dioxane	94	37
9	*SaSa*-**C**	Me	KO*t*Bu	DCM	92	35
10	*SaSa*-**C**	Me	KO*t*Bu	Hexane	<20	N.D.
11	*SaSa*-**C**	Me	NaO*t*Bu	Toluene	43	35
12	*SaSa*-**C**	Me	LiO*t*Bu	Toluene	<15	N.D.
13	*SaSa*-**C**	Me	KHMDS	Toluene	<10	N.D.

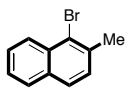
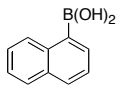
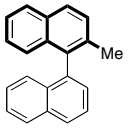
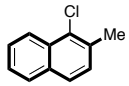
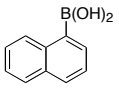
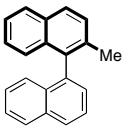
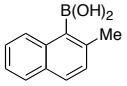
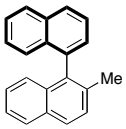
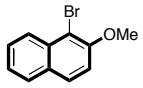
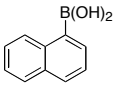
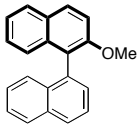
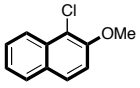
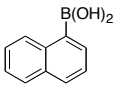
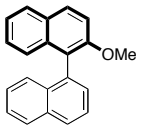
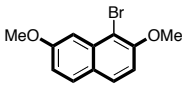
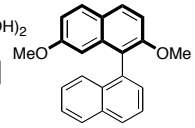
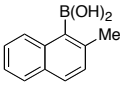
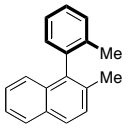
[a] Conditions: bromide (0.125 mmol, 1eq), 2-naphthylboronic acid (1.5 eq), base (2.5 eq), Pd complex (2 mol%), solvent (1 ml), 25^0C, 16 h; [b] Isolated yield; [c] Determined by HPLC.

With the optimized condition in hand [2 mol% of the catalyst (*Sa,Sa*)-**C**, toluene as solvent and KO*t*Bu as base], different substrates were tested and the results are summarized in Table 2. In most of the cases, excellent yields could be obtained by using 2 mol% of the (*Sa,Sa*)-**C**. The coupling of 1-bromo-2-methylnaphthalene and

1-naphthylboronic acid afforded the product in excellent yield and 51% ee (entry 1). Increasing the amount of boronic acid, base and the catalyst decreased the reactivity and selectivity (entry 2). The use of the (*Ra,Ra*)-**C** isomer or the in situ generated

Table 2. Substrate scope of asymmetric Suzuki-Miyaura couplings[a]



Entry	ArX	$ArB(OH)_2$	Ar-Ar	Yield[b]	ee[c]
1				94	51 (*S*)
2				90	43 (*S*)[d]
3				85	30 (*S*)[e]
4				95	27 (*S*)[f]
5				66	33 (*S*)
6				93	46 (*S*)
7				91	60 (*R*)
8				70	50 (*R*)
9				86	12
10				83	28

[a] Conditions: ArX (0.125 mmol, 1eq), $ArB(OH)_2$ (1.5 eq), KO*t*Bu (2.5 eq), (*Sa,Sa*)-**C** (2 mol%), Toluene (1 ml), 25 ^{0}C, 16h; [b] Isolated yield; [c] Determined by HPLC. The absolute configuration was assigned by comparison with literature; [d] $ArB(OH)_2$ (2.5 eq), KO*t*Bu (3.5 eq), (*Sa,Sa*)-**C** (5 mol%); [e] (*Ra,Ra*)-**C** (2 mol%), 50 ^{0}C; [f] **B** (5 mol%), $[Pd(cinnamyl)Cl]_2$ (2.5 mol%).

catalyst (employing the diastereomeric mixture of **B**) lowered the enantioselectivity (entries 3 and 4) as well. The aryl chloride analogue could serve as an effective electrophile, although the yields and enantioselectivities decreased compared to the bromides (entry 1 vs 5, 7 vs 8). Interchanging the electrophile and nucleophile of entry 1 (see entry 6) did not affect the yield, but the ee decreased slightly from 51% to 46%. Interestingly, the configuration of the product was retained (both *S*) which is consistant with Lassaletta's result.[10e] Introduction of the substitution to the 7- position of the electrophile seems to be very deleterious to the selectivity (entry 7 vs 9). One example of *ortho*-substituted phenylbromide was examined, and the product 2-methyl-1-(2- methylphenyl)naphthalene was obtained in good yield (83%) and relatively low ee (28%, entry 10).

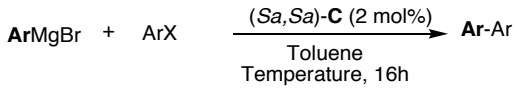
With the promising results from asymmetric Suzuki-Miyaura coupling in hand, we turned our attention to another versatile coupling — the Kumada coupling. We were delighted to find that our catalyst (*Sa,Sa*)-**C** could promote the asymmetric Kumada coupling smoothly giving the chiral biaryls in good yields, albeit in very moderate selectivities (Table 3). For instance, the *in situ* generated 2-methoxynaphthylmagnesium bromide can couple with 1-bromonaphthalene at room temperature affording the chiral binaphthyl product in 81% yield and 48% ee (entry 1). In this case, switching the nucleophile and electrophile to each other reduced both reactivity and selectivity, but not the configuration of the product (entry 2). Using aryl chloride retained the selectivity, although the yield of the product decreased dramatically from 81% to 40% (entry 3 vs 1). Replacement of 1-bromonaphthalene with 2-methylphenylbromide lowered both the yield and enantioselectivity (entry 4 vs 1). The yield was improved by heating (50 °C), but at the expense of further eroding the enantioselectivity (31% ee, entry 5). Using the aryl chloride did not change the outcome in terms of reactivity and selectivity (entry 6). Changing the nucleophile to a more sterically hindered compound (2-methylnaphthylmagnesium bromide) decreased the enantioselectivity (27% ee, entry 7 vs 1).

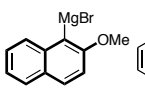
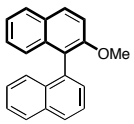
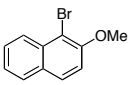
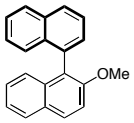
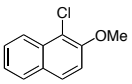
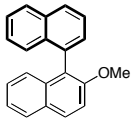
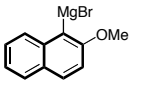
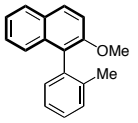
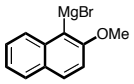
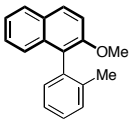
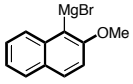
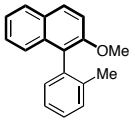
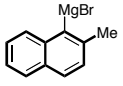
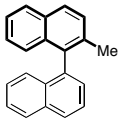
5.4 Conclusion

In conclusion, we report the synthesis of a new NHC ligand with a chiral *N*-heterocycle and naphthyl side chains having 4-heptyl groups in the 2-position. The

imidazolinium salts showed the existence of three different isomers in such NHC structures. Diastereomerically pure palladium complexes incorporating these ligands were obtained after simple chromatography. One of the resulting compounds (*Sa,Sa*-**C**) was tested in the asymmetric Suzuki-Miyaura and Kumada coupling that formed chiral biaryls in high yields and moderate enantioselectivities. This represents the first example of asymmetric C-C couplings giving chiral biaryls using a monodentate chiral NHC ligand.

Table 3. Substrate scope of asymmetric Kumada coupling[a]



Entry	ArMgBr	Ar'X	Temp.(°C)	Ar-Ar'	Yield[b]	ee[c]
1			RT		81	48 (*R*)
2[d]			50		72	37(*R*)
3			50		40	41 (*R*)
4			RT		51	39
5[d]			50		71	31
6[d]			50		77	31
7			RT		78	27 (*S*)

[a] Conditions: ArMgBr (0.25 mmol, 1 eq), Ar'X (1.0 or 2.0 eq), (*Sa,Sa*)-**C** (2 mol%), THF (2 ml), 16h; [b] Isolated yield; [c] Determined by HPLC. The absolute configuration was assigned by comparison with literature; [d] 2.0 equivalents of halide was used.

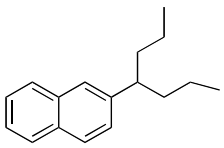
Acknowledgment. Support for this work was provided by the SNF (grant to L. Wu), by the University of Zurich and by the University of Western Australia.

5.5 Experimental Part

General: All reactions were carried out using standard Schlenk or glovebox (Mecaplex or Innovative Technology) techniques under nitrogen. KO*t*Bu was used after sublimation. All other reagents were used as received unless otherwise noted. Solvents were purchased in the best quality available, degassed by purging thoroughly with nitrogen and dried over molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Solvents for NMR spectroscopy were degassed with nitrogen and dried over molecular sieves. NMR spectra were collected on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra were calibrated to the residual 1H and 13C of the solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). High-resolution electrospray ionization mass spectrometry was performed on a *FinniganMAT 900* (Finnigan MAT95, San Jose, CA; USA) double-focusing magnetic sector mass spectrometer (geometry BE). Crystallographic data for the structure were collected at 100(2) K on an Oxford Diffraction Gemini diffractometer fitted with Mo Kα radiation.

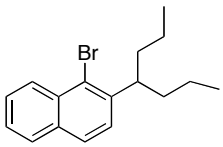
Synthesis of the Pd complex:

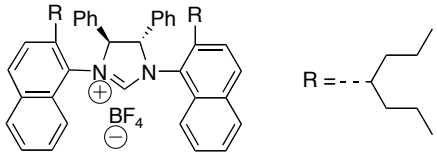
2-(4-heptyl)naphthalene. In a 250 mL 3-necked flask, equipped with condenser, addition funnel and N_2 inlet, were added magnesium (1.18 g, 48.3 mmol) and I_2 (one crystal) under N_2. In the addition funnel were charged 2-bromonaphthalene (10.00 g, 48.3 mmol) and THF (70 ml). A small amount of this solution was added to the flask and warmed with the heat gun until the color became light brown. The reaction mixture was then heated to 60˚C (oil bath) and the remaining 2-bromonaphthalene solution was added dropwise. At the end of the addition, the mixture was further refluxed for 1h. In the meanwhile, in a 250 ml Schlenk flask containing 60 ml of dry THF where charged 4-bromoheptane (6.66 g, 37.2 mmol) and $(FeCl_3)_2(TMEDA)_3$ (0.75 g, 1.12 mmol). To this flask was then



added dropwise the Grignard reagent previously generated; the resulting black mixture was stirred for 30 min at room temperature. The reaction was quenched with aqueous HCl (1 M solution) and extracted with Et_2O (2x150 ml). After evaporation of the solvent, the crude product was heated at 90 °C under high vacuum to eliminate the excess of alkyl bromide and naphthalene. The desired product was isolated after flash chromatography (eluent: hexane) as colorless oil (7.3 g, 92 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (m, 3H), 7.61 (s, 1H), 7.52-7.42 (m, 2H), 7.37 (m, 1H), 2.76 (m, 1H), 1.77-1.64 (m, 4H), 1.30-1.15 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 133.9, 132.5, 128.1, 127.9, 127.8, 126.6, 126.3, 126.0, 125.2, 45.9, 39.4, 21.1, 14.4. HRMS (ESI) *m/z* calcd for $C_{17}H_{22}$: 226.1722. Found: 226.1722.

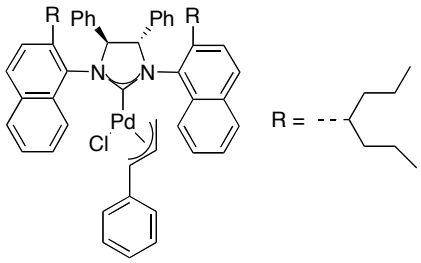
1-bromo-2-(4-heptyl)naphthalene. 2-(4-heptyl)naphthalene (5.00 g, 23.55 mmol) was dissolved in 100 ml of dry CH_2Cl_2 in a Schlenk flask and the solution was cooled to -78°C. At this temperature a solution of Br_2 (3.76 g, 23.55 mmol) in CH_2Cl_2 (50 ml) was slowly added. The reaction was left stirring at the same temperature for 5 hours and was subsequently quenched with aqueous NaOH (1M solution, 100 ml). The organic phase was separated, washed with 200 ml of water, dried with $MgSO_4$, filtered and concentrated under vacuum to afford a orange oil. After purification on a silica gel pad (eluent: hexane) to eliminate residual Br_2, the desired product was obtained as a colorless oil (6.80 g, 99 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.78 (m, 2H), 7.57 (t, *J* = 8.3 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 3.63 (m, 1H), 1.77-1.51 (m, 4H), 1.34-1.08 (m, 4H), 0.85 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 133.5, 132.8, 128.3, 128.2, 128.0, 127.4, 126.0, 125.3, 125.2, 44.2, 39.1, 20.7, 14.5. HRMS (EI) *m/z* calcd for $C_{17}H_{21}Br$ 304.0827. Found: 304.0830.



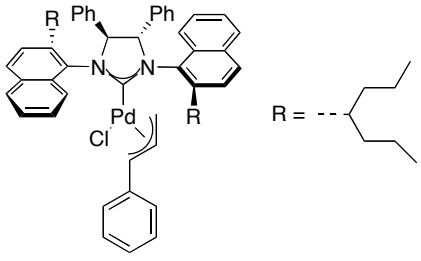


4*S*,5*S*-1,3-Bis[2-(4-heptyl)]-4,5-diphenyl-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate [B, (*2*)-DiPhSIHeptNap·HBF$_4$]. A 500 mL schlenk flask was charged with Pd(dba)$_2$ (472 mg, 0.82 mmol), (±)-BINAP (610 mg, 0.98 mmol), NaO^{t}Bu (2.36 g, 24.6 mmol) and toluene (200 mL) and stirred for 5 min. 1-Bromo-2-(4-heptyl)-naphthalene (5.0 g, 16.4 mmol) and (*1S,2S*)-(-)-1,2-diphenylethylenediamine (1.65 g, 7.80 mmol) were then added and the reaction mixture was heated to 120 °C for 12 h. After cooling to room temperature, the resulting mixture was filtered through a celite and washed with EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (SiO_2, 1:10-1:3 CH_2Cl_2/*n*-hexane) to afford 1*S*,2*S*-N,N′-bis[2-(4-heptyl)-naphthalen-1-yl]-1,2-diphenylethane-1,2-diamine as a pale yellow foam (2.32 g, 45%). 1*S*,2*S*-N,N'-Bis[2-(4-heptyl)naphthalen-1-yl]-1,2-diphenylethane-1,2-diamine (500 mg, 0.76 mmol), ammonium tetrafluoroborate (119 mg, 1.14 mmol), triethyl orthoformate (5 ml) and formic acid (1 drop) were heated to 110 °C and stirred for 12 h. The resulting brown solution was dried in vacuo, and the residue was purified by chromatograph (hexane:diethylether 10:1) to get a yellow solid which was dissolved in 4 ml of diethylether. To this solution was added hexane to get the title product as a white solid (310 mg, 54%). ^{1}H NMR ($CDCl_3$, 500 MHz) exists as a mixture of three atropisomers (28:34:38): δ 8.44-7.14 (m, NC*H*N and Ar*H*) (correspond to the three atropisomers of 23 protons), {6.70 (s, NC*H*Ph), 6.58 (d, *J* = 12.8 Hz, NC*H*Ph), 6.23 (s, NC*H*Ph), 6.21 (d, *J* = 12.8 Hz, NC*H*Ph) (correspond to the three atropisomers of 2 protons)}, 3.38-2.68 (m, C*H*Nap) (correspond to the three atropisomers of 2 protons), 2.19-0.12 (m, *4-heptyl*) (correspond to the three atropisomers of 28 protons)}. ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 159.01, 158.75, 157.96, 145.01, 143.71, 142.68, 141.80, 132.96, 132.81, 132.61, 132.49, 132.42, 132.35, 132.19, 132.10, 131.22, 131.07, 130.65, 130.61, 130.36, 130.21, 130.11, 129.93, 129.87, 129.80, 129.76, 129.70, 129.63, 129.39, 129.36, 129.08, 128.88, 128.84, 128.60, 128.43, 128.18, 128.05, 127.66, 127.40, 127.34, 127.01, 126.39, 126.30, 125.49, 125.44, 124.76, 124.23, 124.12, 123.75, 122.02, 121.03, 121.00, 120.03, 75.87, 74.53, 73.27, 42.33,

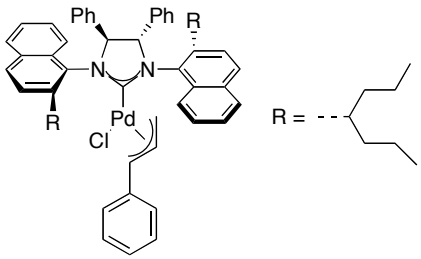
42.10, 41.04, 40.73, 38.92, 38.85, 38.41, 38.21, 37.78, 37.76, 37.15, 37.11, 22.20, 22.08, 21.90, 21.84, 21.08, 21.05, 20.97, 20.58, 14.79, 14.78, 14.42, 14.41, 14.37, 14.24, 14.18. HRMS (ESI): *m/z* : calcd for $C_{49}H_{55}N_2$[M-BF]$^+$: 695.4360; found: 695.4356.



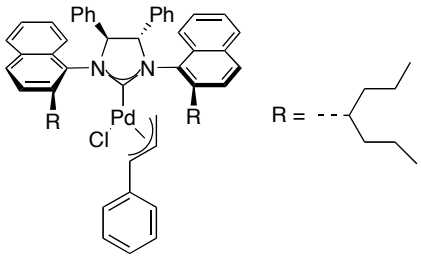
Chloro[(1,2,3-n)-3-phenyl-2-propenyl][*4S*,*5S*-*1*,3-Bis(2-(1-propylbutyl)-naphthalen-1-yl)-4,5-dihydro-4,5-diphenyl imidazol-2-ylidene] palladium(II) [((*2,7*)-DiPhSI(4-Hep)Nap)Pd(cin)Cl]. (*2*)-DiPhSI(4-Hep)tNap·HBF_4 (340 mg, 0.45 mmol), KO*t*Bu (53 mg, 0.47 mmol) and [Pd(cinnamyl)Cl]$_2$ (117 mg, 0.23 mmol) were mixed together in a round flask in the glovebox. Dry THF (45 mL) was added and the mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was separated by flash chromatography on siliga gel (n-hexane:EtOAc 10:1) to afford the title product as a yellow solid (220 mg, 53%). Elemental analysis: calcd for $C_{58}H_{63}ClN_2Pd$: C, 74.90; H, 6.83; N, 3.01. Found: C, 75.43; H, 7.02; N, 2.89. HRMS (ESI): *m/z* : calcd for $C_{58}H_{63}N_2Pd$ [M-Cl]+: 893.4040; found: 893.4048.



Data for (*Sa,Sa*)-**C** are as follows (100 mg). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.50 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.41-6.88 (m, 19H), 6.43 (d, *J* = 7.1 Hz, 2H), 5.68 (s, 2H), 3.90-3.47 (br m, 4H), 2.18-0.80 (m, 30H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.59, 138.64, 138.16, 132.92, 132.64, 131.56, 128.99, 128.94, 128.87, 128.82, 128.75, 128.68, 127.89, 127.76, 127.16, 127.13, 126.23, 125.52, 125.32, 125.06, 109.55, 77.85, 49.40, 39.61, 39.27, 38.59, 29.66, 20.69, 14.99, 14.88.



Data for (*Ra,Ra*)-**C** are as follows (70 mg). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.50 (br, 2H), 7.90-7.02 (br m, 25H), 6.05 (s, 2H), 5.10-3.42 (br m, 4H), 2.42-0.15 (br m, 30H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.44, 193.72, 152.80, 145.06, 137.28, 133.01, 132.65, 131.28, 131.03, 129.36, 129.27, 129.12, 129.07, 128.95, 128.81, 128.77, 128.63, 128.49, 128.37, 128.15, 127.99, 127.90, 127.77, 127.53, 127.21, 126.73, 126.26, 125.94, 125.45, 109.01, 92.42, 77.87, 74.44, 47.10, 41.36, 38.75, 37.96, 35.88, 34.68, 34.53, 31.60, 29.07, 26.92, 25.29, 22.70, 22.66, 22.63, 20.72, 15.04, 14.49, 11.44.



Data for (*Ra,Sa*)-**C** are as follows (50 mg). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.54 (d, *J* = 8.5 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.84-6.93 (m, 25H), 6.10 (br, 1H), 5.65 (br, 1H), 4.36-3.33 (m, 4H), 2.51-0.24 (m, 30H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 215.15, 145.37, 138.05, 133.16, 132.86, 131.77, 130.74, 129.04, 128.95, 128.89, 128.83, 128.73, 128.65, 128.50, 128.28, 127.93, 127.67, 127.22, 127.08, 126.33, 126.18, 125.56, 88.48, 53.44, 40.04, 39.05, 38.14, 37.94, 37.64, 20.60, 19.96, 15.02, 14.78, 14.66, 14.58.

Asymmetric Cross Coupling:

General Protocol for the asymmetric Suzuki-Miyaura Coupling

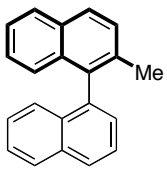
In the glovebox, arylhalide (0.125 mmol, 1.0 eq.), boronic acid (1.5 eq.), KO*t*Bu (2.5 eq.) and palladium complex (2.3 mg, 2 mol%) were mixed in 1.0 ml toluene in a vial (10 mL screw-cap threaded). The whole mixture was stirred at room temperature for

16 h before quenching with 5 ml H_2O ouside the glovebox. The mixture was extracted with diethylether (3 x 5ml) before drying with anhydrous $MgSO_4$. After drying on a rotary evaporator, the residue was purified by column chromatography. The ee value was determined by HPLC.

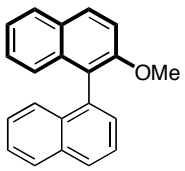
General Protocol for the asymmetric Kumada Coupling

In the glovebox, a vial (10 mL screw-cap threaded) equipped with a stir-bar was charged with arylhalide (0.25 mmol, 1eq.), Mg (6.6 mg, 0.28 mmol) and 2.0 ml THF. Then the whole mixture was heated to 70 ^{0}C for 2 h before cooling to room temperature. Inside the glovebox, palladium complex (4.6 mg, 2 mol%) and the other arylhalide (1.0 or 2.0 eq) were added to the formed Grignard reagent. The mixture was stirred at room temperature (or heated to the corresponding temperature outside glovebox) for 16 h before quenching with 5ml of water. Extraction with diethylether (3 x 5ml) was followed by drying with anhydrous $MgSO_4$. After drying on a rotary evaporator, the residue was purified by column chromatography. The ee value was determined by HPLC.

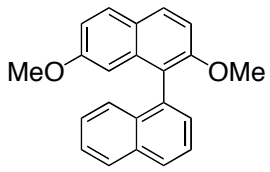
(Table 2, entry 1) 94% yield, 51% ee. The spectral data were in accordance with those reported in the literature.[10i] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.01 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 3.0 Hz, 1H), 7.93 (d, J = 3.2 Hz, 1H), 7.66 (dd, J = 8.2, 7.0 Hz, 1H), 7.56-7.51 (m, 2H), 7.46-7.43 (m, 2H), 7.32-7.21 (m, 4H), 2.18 (s, 3H). HPLC: Chiralcel OJ-H Column (250 mm); detected at 224 nm; n-hexane / *i*-propanol = 95/5; flow = 1.0 mL/min; Retention time: 6.4 min (major), 9.6 min (minor). The absolute configuration was assigned by comparison with literature data.[18]



(Table 2, entry 7) 91% yield, 60% ee. The spectral data were in accordance with those reported in the literature.[10e] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.03-7.97 (m, 3H), 7.91 (d, J = 8.2 Hz, 1H), 7.65 (dd, J = 8.2, 7.0 Hz, 1H), 7.51-7.46 (m, 3H), 7.38-7.19 (m, 5H), 3.80 (s, 3H). HPLC: Chiralpak AD-H Column (250 mm); detected at 224 nm; n-hexane / *i*-propanol = 95/5; flow = 0.25 mL/min; Retention time: 18.2 min (minor), 20.1 min (major). The absolute configuration was assigned by comparison with literature

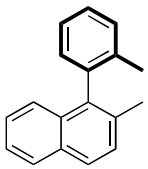


data.[10d]

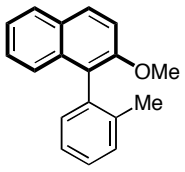


(Table 2, entry 9) 86% yield, 12% ee.^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.99-7.93 (m, 3H), 7.81 (d, J = 8.9 Hz, 1H), 7.66 (dd, J = 8.2, 7.2 Hz, 1H), 7.51-7.32 (m, 5H), 7.04 (dd, J =8.9, 2.4 Hz, 1H), 6.49 (d, J = 2.5 Hz, 1H), 3.79 (s, 3H), 3.52 (s, 3H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 158.06, 155.23, 135.55, 134.73, 133.75, 132.78, 129.39, 129.14, 128.36, 128.19, 127.70, 126.15, 125.76, 125.63, 124.61, 122.16, 116.12, 111.13, 104.00, 56.57, 54.95. HRMS (ESI): *m/z* : calcd for $C_{22}H_{18}O_2[M]^+$: 314.1307; found: 314.1309. HPLC: Chiralpak AD-H Column (250 mm); detected at 224 nm; n-hexane/*i*-propanol = 95/5; flow = 0.25 mL/min; Retention time: 22.0 min (minor), 23.2 min (major).

(Table 2, entry 10) 83% yield, 28% ee. The spectral data were in accordance with those reported in the literature.[10F] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 (dd, J = 8.1, 0.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.47-7.28 (m, 7H), 7.16 (d, J = 8.0 Hz, 1H), 2.2 (s, 3H), 1.96 (s, 3H). HPLC: Chiralcel OJ-H Column (250 mm); detected at 224 nm; n-hexane / *i*-propanol = 100/0; flow = 0.50 mL/min; Retention time: 12.9 min (major), 17.8 min (minor).



(Table 3, entry 4) 51% yield, 39% ee. The spectral data were in accordance with those reported in the literature.[19] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (d, J = 9.0 Hz, 1H), 7.88-7.86 (m, 1H), 7.43-7.26 (m, 7H), 7.24 (d, J = 8.0 Hz, 1H), 3.88 (s, 3H), 2.04 (s, 3H). HPLC: Chiralcel OJ-H Column (250 mm); detected at 224 nm; n-hexane / *i*-propanol = 95/5; flow = 0.50 mL/min; Retention time: 15.2 min (minor), 20.4 min (major).



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